Specification.

Diazepane derivatives or salts thereof

The field of technology.

This invention relates to novel diazepane derivatives or salts thereof useful as drug, in particular as activated blood coagulation factor X inhibitor, and the drug thereof.

Background technology.

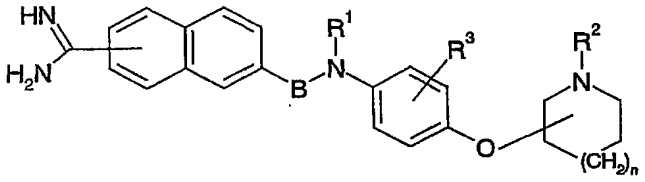
In recent years, accompanied by the Westernisation of the life style and increase in elderly population, thrombotic obstructive diseases such as myocardial infarction, cerebral thrombosis, peripheral arteriothrombosis are on the increase year by year, and the social importance of its treatment is becoming more and more important. Anticoaglulant therapy is one of the internal medical therapy of the treatment and prevention of thrombosis together with the fibriolysis therapy and anti-platelet therapy (Sogo Rinsyo 41: 2141-2145, 1989). In particular, for the prevention of thrombosis, the safety that can withstand the long term administration and expression of concrete and also appropriate anticoagluant activity are essential. Potassium warfarin is widely used all over the world as the only oral anticoagulant, however, because of the properties based on its action mechanism, the control of the anticoagulant ability is difficult (J. Clinical Pharmacology, 32, 196-209, 1992 and N. Eng. J. Med. 324 (26) 1865-1875, 1991), and it is a drug very difficult to use clinically, and emergence of more useful and easy to use anticoagulant is desired.

Thrombin not only controls the conversion of fibrinogen to fibrin which is the final stage of coagulation, but also is deeply involved in the activation and aggregation of platelet (Satoru MATSUO ed., T-PA and Pro-UK, Gakusai Kikaku, pp. 5-40, Blood coagulation, 1986), and its inhibitor has been in the centre of the anticoagulant research for a long time as the target for drug creation. However, the bioavailability for oral administration is low, and there is also a problem in the safety aspect (Biomed. Biochim. Acta, 44, 1201-1210, 1985), and thrombin inhibitor that can be orally administered is not available on the market at present.

The Activated blood coagulation factor X is a key enzyme positioned at the confluence point of the exogenous and endogenous coagulation cascade reaction, and because it is positioned at the upstream of thrombin, it is possible that the inhibition of this factor is more efficient than inhibition of thrombin and also the coagulation system can be specifically inhibited (Thrombosis Research (19), 339-349, 1980).

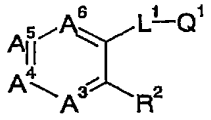
As compound showing activated blood coagulation factor X inhibitory action, amidinonaphthylalkylbenzene derivatives or salts thereof are known (Kokai 5-208946, Thrombosis Haemostasis 71(3), 314-319, 1994 and Thrombosis Haemostasis 71(3), 393-396, 1994).

Moreover, in WO96/16940, amidinonaphthyl derivatives or salts thereof represented by the following general formula are described as compounds showing activated blood coagulation factor X inhibitory action (prior art technology 1).



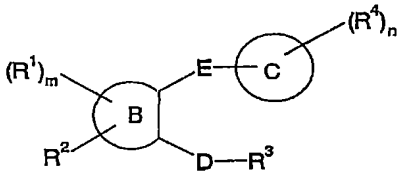
(cf. the specification for symbols in the formula)

Moreover, in WO99/00121, WO99/00126, WO99/00127, WO99/00128, WO00/39111, WO00/39117 and WO00/39118, phenylenediamide compounds and the like represented by the following general formula are described as factor Xa inhibitor (prior art technology 2).



(cf. the specification for symbols in the formula)

Furthermore, in WO99/32477, a wide ranging compounds represented by the following general formula are described as anticoagulant (prior art technology 3).

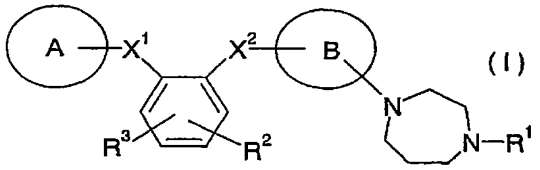


(cf. the specification for symbols in the formula)

Indication of Invention

The inventors of this invention created the diazepane derivatives or salts thereof represented by the following general formula (I), and discovered that these had excellent activated blood coagulation factor X inhibitory action, in particular had excellent per oral activity.

In other words, this invention relates to diazepane derivatives or salts thereof represented by the following general formula (I), and drug composition having these as effective component, in particular an activated blood coagulation factor X inhibitor.



(The symbols in above formula have the following meanings.
A ring and B ring: may be the same or different and denote aryl or heteroaryl each of which may have 1-3 substituents,
X1: -C(=O)=NR4-, -NR4-C(=O)-, -NR4-CH2-, -O-CH2-, -CH2-CH2, or -CH=CH-,
X2: -C(=O)=NR5-, or -NR5-C(=O)-,
R1: hydrogen atom, lower alkyl, -lower alkylene-O-lower alkyl, C3-8 cycloalkyl, aryl, heteroaryl, -lower alkylene-C3-8 cycloalkyl, -lower alkylene-aryl, -lower alkylene-heteroaryl, or -C(=NR6)-lower alkyl,
R2: -OH, -O-lower alkyl, -O-lower alkylene-OH, -O-SO2-OH, -O-lower alkylene-COOH, O-lower alkylene-COO-lower alkyl, -COOH, -COO-lower alkyl, or halogen atom,
R3: hydrogen atom, halogen atom, or lower alkyl,
R4, R5, and R6: may be the same or different and denote hydrogen atom, or lower alkyl)

The compound of this invention (I) differs from the structure of the compound described in prior art technology 1, for the point of having diazepan-1-yl group, the point of having at least 4 ring structure, the point in which the nitrogen atom of diazepane is directly bonded to the B ring, and the like. Moreover, the compound of this invention (I) differs from the structure of the compound described in prior art technology 2, for the point of having diazepan-1-yl group. Furthermore, in the prior art technology 3, no compound having diazepan-1-yl group is described in embodiments. in other words, the chemical structural characteristics of the compound of this invention (I) is that the diazepanylaryl or diazepanylheteroaryl is bonded to benzene ring via amide bond and the like, and also said benzene ring is bonded to aryl or heteroaryl via abide bond and the like, and also said benzene ring has -OH, -O-lower alkyl, or halogen and the like.

Below, the compound of this invention (I) is described in detail.

In the definition of general formula in this specification, the term "lower" means a straight chain or branched carbon chain of carbon number 1-6 unless specifically stated. Accordingly, as lower alkyl in R1-R6 and substituent exemplified later, for example, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, isopentyl, neopentyl, tert-pentyl, 1-methylbutyl, 2-methylbutyl, 1,2-dimethylpropyl, hexyl, isohexyl, 1-methylpenttyl, 2-methylpenttyl, 3-methylpenttyl, 1,1-dimethylbutyl, 1,2-dimethylbutyl, 2,2-dimethylbutyl, 1,3-dimethylbutyl, 2,3-dimethylbutyl, 3,3-dimethylbutyl, 1-ethylbutyl, 2-ethylbutyl, 1,1,2-trimethylpropyl, 1,2,2-trimethylpropyl, 1-ethyl-1-methylpropyl, 1-ethyl-2-methylpropyl, and the like are nominated. Among these, ones having carbon number 1-3 are preferred, and methyl and ethyl are particularly preferred.

The "lower alkylene" denotes C1-6 alkylene wherein an arbitrary hydrogen atom is removed from aforesaid "lower alkyl", and methylene, ethylene, propylene, isopropylene are preferred.

The "aryl" means aromatic hydrocarbon ring including condensed ring, preferably aryl of carbon number 6-14, more preferably phenyl, naphthyl and the like are nominated.

The "heteroaryl" means heterocyclic aryl including condensed ring having 1-4 hetero atms which may be the same or different and selected from N, S and O, and in embodiments, furyl, thienyl, pyrrolyl, imidazolyl, pyrazolyl, isothiazolyl, isoxazolyl, triazolyl, tetrazolyl, pyridyl, pyrimidinyl, pyridazinyl, pyrazinyl, indolyl, indazolyl, indolizinyl, quinolyl, isoquinolyl, quinazolinyl, quinolidinyl, quinoxalinyl, cinnolinyl, benzimidazolyl, imidazopyridyl, benzofuranyl, dihydrobenzofuranyl, naphthylidinyl, 1,2-benzoisoxazolyl, benzoxazolyl, benzothiazolyl, oxazolopyridyl, isothiazolopyridyl, benzothienyl and the like are nominated, however it is not limited to these.

The "C3-8 cycloalkyl" denotes cycloalkyl of carbon number 3-8, and in particular, cyclopropyl and cyclobutyl are preferred.

As "substituent" of the "aryl or heteroaryl each of which may have 1-3 substituents", optionally substituted lower alkyl, lower alkenyl, lower alkynyl, C3-8 cycloalkyl, -O-optionally substituted lower alkyl, halogen atom, -NH2, -NH-lower alkyl, -N-(lower alkyl)2, -C(=NH)-NH2, -C(=N-OH)-NH2, -C(=NH)-NH-OH, -C(=NH)-NH-C(=O)-O-lower alkyl, -COOH, -C(=O)-O-optionally substituted lower alkyl, -C(=O)-O-optionally substituted C6-14 aryl, -C(=O)-O-optionally substituted heteroaryl, -CN, -NO2, -OH, -O-CO-optionally substituted lower alkyl, -O-CO-NH2, -O-CO-NH-

lower alkyl, -O-CO-N-(lower alkyl)2, -SH, -C(=O)-NH2, -C(=O)-NH-(lower alkyl), -C(=O)-N-(lower alkyl)2 and the like are nominated.

As "substituent" of the "optionally substituted lower alkyl, lower alkenyl, lower alkynyl, C3-8 cycloalkyl", "optionally substituted C6-14 aryl", or "optionally substituted heteroaryl", halogen atom, -COOH, -C(=O)=O+lower alkyl, -OH, -NH2, -NH-lower alkyl, -N-(lower alkyl)2 and the like are nominated. As "halogen atom", fluorine atom, chlorine atom, iodine atom, bromine atom are nominated. In particular, chlorine atom and bromine atom are preferred.

Moreover, as R1, a lower alkyl is preferred, in particular methyl is preferred. As R2, -OH is in particular preferred. R4-R6 may be the same or different and denote hydrogen atom or lower alkyl, however, hydrogen atom is more preferred. Moreover, as X1, -C(=O)-NR4-, -NR4-C(=O)-, -NR4-CH2- and -O-CH2-are preferred, and -C(=O)-NR4- and -NR4-C(=O)- are particularly preferred. X2 denotes -C(=O)-NR5- or -NR5-C(=O)-, and -NR5-C(=O)- is more preferred.

The A ring and B ring may be the same or different and preferably benzene ring, pyridine ring, naphthalene ring, thiophene ring, benzofuran ring or quinoline ring. In particular, benzene ring is preferred.

Among the compounds of this invention, the embodiments of particularly preferred compounds are 3-hydroxy-4'-methoxy-2-{[4-(4-methyl-1,4-diazepan-1-yl) benzoyl] amino} benzanilide, 3-hydroxy-N1-(4-methoxybenzoyl)-N2-[4-(4-methyl-1,4-diazepan-1-yl) benzoyl]-1,2-phenylenediamine, 5-chloro-N-(5-chloro-2-pyridyl)-3-hydroxy-2-{[4-(4-methyl-1,4-diazepan-1-yl) benzoyl] amino} benzamide, 5-chloro-3-hydroxy-4'-methoxy-2-{[4-(4-methyl-1,4-diazepan-1-yl) benzoyl] amino} benzanilide and 5-bromo-N-(5-chloro-2-pyridyl)-3-hydroxy-2-{[4-(4-methyl-1,4-diazepan-1-yl) benzoyl] amino} benzamide or salts thereof.

Moreover, mixture of geometric isomer, tautomer, various isomers such as optical isomers and isolated one are included in the compound of this invention.

There is a situation that the compound of this invention (I) forms acid addition salt. Moreover, there is a situation depending on kind of substituent that a salt with a base is formed. As such salt, in embodiments, acid addition salts of mineral acid such as hydrochloric acid, hydrobromic acid, hydroiodic acid, sulphuric acid, nitric acid, phosphoric acid and the like, organic acid such as formic acid, acetic acid, propionic acid, oxalic acid, malonic acid, succinic acid, fumaric acid, maleic acid,

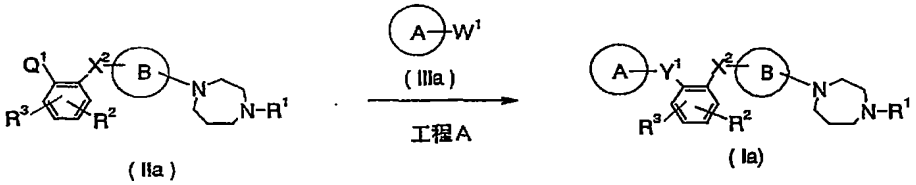
lactic acid, malic acid, tartaric acid, citric acid, methanesulfonic acid, ethanesulfonic acid, and the like, acidic amino acid such as aspartic acid, glutamic acid and the like, salt with inorganic base such as sodium, potassium, magnesium, calcium, aluminium and the like, organic base such as methylamine, ethylamine, ethanolamine and the like, basic amino acid such as lysine, ornithines and the like, and ammonium salt and the like are nominated.

Furthermore, a hydrate of the compound (I), pharmaceutically acceptable various solvates and the crystal polymorphism are included in this invention. Moreover naturally this invention is not restricted to the compounds described in later-described Examples but includes all diazepane derivatives represented by the general formula (I) or pharmaceutically acceptable salts thereof.

Moreover the compounds of this invention include all the compound the is converted to compound of aforesaid (I) or a salt thereof by metabolism in vivo, so called prodrug. As the group forming the prodrug of this compound, groups described in Prog. Med. 5: 2157-2161 (1985) and groups described in "Drug development" vol. 7, molecular design pp. 163-198, Hirokawa Shoten (1990) are nominated.

(A process for the production)
Below a typical process for the production of the compound of this invention is described.

Step A



(wherein, A, B, R1, R2, R3 and X2 have aforesaid meanings, and, as for Q1, W1, when Q1 denotes -NHR4, then W1 denotes -COOH, and when Q1 denotes -COOH, then W1 denotes -NHR4. Y denotes -C(=O)-NR4- or -NR4-C(=O)-. R4 has aforesaid meaning.)

Step A

It is a reaction wherein carboxylic acid and the amine in a combination of compound (IIa) and compound (IIIa) are reacted preferably in the presence of condensing agent and the compound (Ia) is synthesised. This reaction can be carried out following acylation reaction of conventional method.

As condensing agent, N,N-dicyclohexylcarbodiimide (DCC), 1-ethyl-3-(3-(N,N-dimethylamino) propyl) carbodiimide, carbonyldiimidazole, diphenylphosphoryl azide (DPPA) or diethyl phosphoryl cyanide and the like can be suitably used.

Moreover, carboxylic acid is derived to corresponding active derivative of carboxylic acid, thereafter it can be condensed with amine.

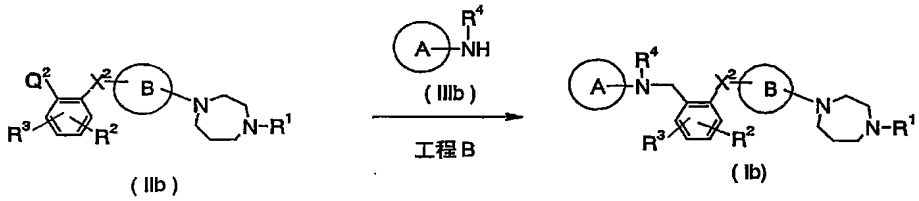
As active derivative of carboxylic acid to be used, active ester obtained by reaction with the compound of phenolic system of for example p-nitrophenol and the like, the compound of N-hydroxyamine system of for example 1-hydroxy succinimide, 1-hydroxybenzotriazole and the like; carbonic acid mono alkyl ester or mixed acid anhydride obtained by reaction with organic acid or phosphoric acid system mixed acid anhydride obtained by reaction with diphenylphosphoryl chloride, N-methylmorpholine; acid azide obtained by reaction of ester with hydrazine, alkyl nitrite; acid halide of for example acid chloride, acid bromide and the like; symmetric acid anhydride and the like are nominated. Usually aforesaid reaction is performed in a solvent under cooling to room temperature, however, there may be a situation that it must be carried out under anhydrous conditions depending on the acylation reaction.

As solvent, a solvent which does not participate in reaction, for example water, ethanaol, methanol, dimethylformamide, dioxane, tetrahydrofuran, ether, dichloroethane, dichloromethane, chloroform, carbon tetrachloride, dimethoxymethane, dimethoxyethane, ethyl acetate, benzene, acetonitrile, dimethylsulfoxide and the like or mixed solvent of these can be used, and it is preferably selected according to the applied process.

Moreover, depending on the applied process, there is a situation that the reaction proceeds smoothly by reacting in the presence of base such as sodium carbonate, potassium carbonate, sodium ethoxide, potassium t-butoxide, 1,8-diazabicyclo [5.4.0] undec-7-ene (DBU), N-methylmorpholine, triethylamine, trimethylamine, pyridine, sodium hydride, butyllithium, sodium amide and the like or using these base as solvent.

Moreover, any method for the reaction for the formation of amide bond can be employed other than the method described here.

Step B



(wherein, A, B, R1, R2, R3, R4 and X2 have aforesaid meanings, and, Q2 denotes -CHO or -CH2-leaving group. As leaving group, halogen group, -O-(SO2)-alkyl, -O-(SO2)-aryl group and the like are nominated.)

Step B

It is a reaction wherein aldehyde and amine or a compound having -CH2-leaving group and amine in a combination of compound (IIb) and compound (IIIb) are condensed and the compound (Ib) is synthesised.

In the case of the combination of aldehyde and amine, this reaction can be carried out in accordance with conventional reductive amination in the presence of reducing agent.

As reducing agent, sodium borohydride, sodium cyanohydride, sodium triacetoxyborohydrate, borane-trimethylamine complex and the like can be suitably used. Moreover, catalytic hydrogenation may be carried out in the presence of catalyst such as palladium-carbon, platinum oxide and the like at ambient pressure to increased pressure. This reaction is carried out in a solvent which is not involved in aforesaid reaction under cooling to warming.

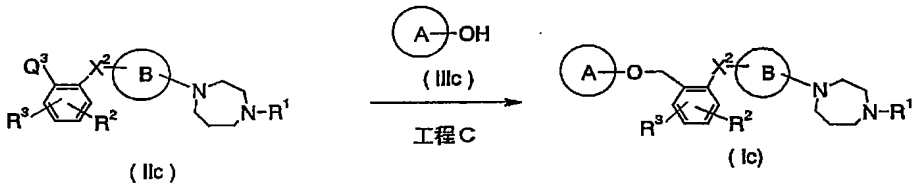
Moreover, depending on the applied process, there is a situation that the reaction proceeds smoothly by reacting in the presence of acid such as acetic acid, toluene sulphonic acid, sulphuric acid and the like or using these as solvent.

In the case of the combination of a compound having -CH2-leaving group and amine, this reaction can be carried out in accordance with well known N-alkylation reaction.

This reaction is carried out in a solvent which is not involved in aforesaid reaction under cooling to warming. Moreover, depending on the applied process, there is a situation that the reaction proceeds smoothly by reacting in the presence of aforesaid base, or using these base as solvent.

Moreover, any method for the reaction for the formation of bond of -NR4-CH2- can be employed other than the method described here.

Step C



(wherein, A, B, R1, R2, R3, and X2 have aforesaid meanings, and, Q3 denotes -CH2-leaving group. As leaving group, halogen group, -O-(SO2)-alkyl, -O-(SO2)-aryl group and the like are nominated.)

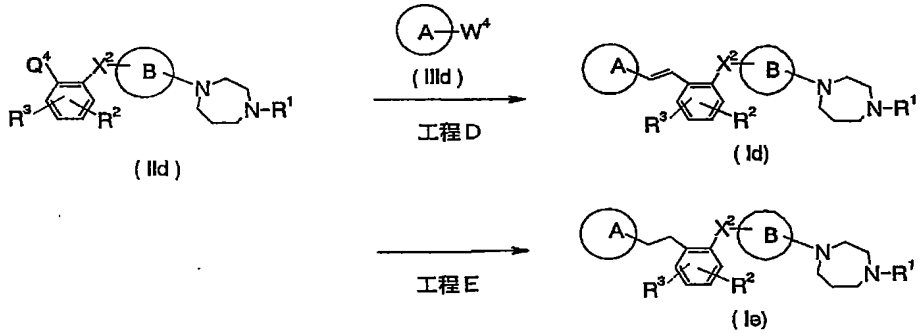
Step C

It is a reaction wherein a compound having -CH2-leaving group and alcohol in a combination of compound (IIc) and compound (IIIc) are condensed and the compound (Ic) is synthesised. This reaction can be carried out in accordance with well known O-alkylation reaction.

This reaction is carried out in a solvent which is not involved in aforesaid reaction under cooling to warming. Moreover, depending on the applied process, there is a situation that the reaction proceeds smoothly by reacting in the presence of aforesaid base, or using these base as solvent.

Moreover, any method for the reaction for the formation of ether bond can be employed other than the method described here.

Step D



Step E

(wherein, A, B, R1, R2, R3, and X2 have aforesaid meanings, and, as for Q4, W4, when Q4 denotes -CHO, then W4 is phosphonium slat such as -CH2-P[+]Ph3Br[-] and the like, phosphorous acid diester such as -CH2-P(=O)(-OEt)2 and the like, or phosphine oxide such as -CH2-P(=O)(-Ph)2 and the like, and when W4 denotes -CHO, then Q4 is phosphonium slat such as -CH2-P[+]Ph3Br[-] and the like, phosphorous acid diester such as -CH2-P(=O)(-OEt)2 and the like, or phosphine oxide such as -CH2-P(=O)(-Ph)2 and the like.)

Step D

It is a reaction wherein aldehyde and phosphonium salt, phosphorous acid diester or phosphine oxide in a combination of compound (IId) and compound (IIId) are reacted in the presence of aforesaid base and the compound (Id) is synthesised. This reaction can be carried out in accordance with well known Wittig reaction or Wittig-Horner reaction.

This reaction is carried out in a solvent which is not involved in aforesaid reaction under cooling to warming. Moreover, depending on the applied process, the intermediate ylide is separated and thereafter it is reacted with aldehyde.

Moreover, any method for the reaction for the formation of carbon-carbon double bond can be employed other than the method described here.

Step E

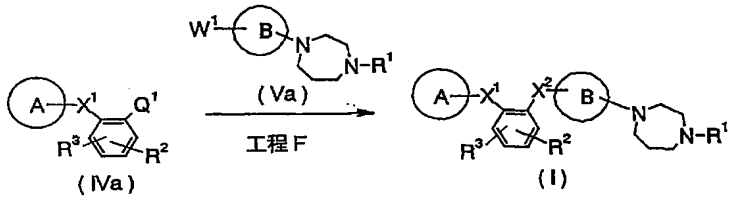
It is a reaction wherein the compound (Ie) is synthesised by reduction reaction of the compound (Id). This reaction can be carried out in accordance with well known hydrogenation reaction using catalyst.

This reaction is carried out under hydrogen atmosphere in a solvent which is not involved in aforesaid reaction under cooling to warming. As catalyst used, palladium-carbon (Pd-C), platinum oxide, Raney nickel, rhodium chlorotriphenylphosphine (Wilkinson catalyst), nickel borate and the like are nominated. Moreover, instead of carrying out under hydrogen atmosphere, ammonium formate, sodium phosphinate, hydrazine and the like can be used as hydrogen source.

Moreover, any method for the reaction for the reduction double bond can be employed other than the method described here.

Moreover, any method for the reaction for the formation of -CH2-CH2 bond can be employed without going through the compound (Id).

Step F



(wherein, A, B, R1, R2, R3, X1, X2, Q1 and W1 have aforesaid meanings.)

Step F

It is a reaction wherein carboxylic acid and amine in a combination of compound (IVa) and compound (Va) are reacted and the compound (I) is synthesised. This reaction is carried out in the same way as in Step A.

Among the compound (I) of this invention, the compound in which the R1 is hydrogen, can also be obtained by carrying out aforesaid hydrogenation reaction and the like using the compound in which R1 in the compound (I) of this invention is benzyl.

Moreover, among the compound (I) of this invention, the compound in which the R1 is other than hydrogen, can also be obtained by carrying out aforesaid well known reductive amination or N-alkylation and the like using the compound in which the R1 in the compound (I) of this invention is hydrogen.

Moreover, among the compound (I) of this invention, the compound in which the R2 is -OH, can also be obtained by synthesising a compound in which its hydroxyl group is protected by a protecting group of phenol, thereafter cleaving by suitable cleaving method for said protecting group. Wherein, the protecting group of phenol is not limited in particular, as long as it is usually used for the protection of phenol, and for example, optionally substituted lower alkyl, aralkyl, tri-lower alkylsilyl, lower alkylcarbonyl, lower alkyloxycarbonyl, sulphonyl and the like are nominated. The "aralkyl" means a group in which hydrogen atom of aforesaid alkyl group is replaced by aryl, and in an embodiment, benzyl, phenylethyl and the like are nominated.

Among the compound (I) of this invention, the compound in which the R2 is -O-lower alkyl, -O-lower alkylene-OH, -O-lower alkylene-COOH, O-lower alkylene-COO-lower alkyl, can be obtained by carrying out aforesaid well known -O-alkylation and the like using the compound in which the R2 in the compound (I) of this invention is -OH. Moreover, the compound in which the R2 in the compound (I) of this invention is -O-SO2-OH can be obtained by sulphonation of the compound in which the R2 in the compound (I) of this invention is -OH using trimethylamine-sulphurtrioxide complex and the like. Furthermore, when an ester group is present in R2, a compound in which the R2 is carboxyl group can be obtained by hydrolysis under acidic condition such as aqueous hydrochloric acid and the like or basic condition such as aqueous sodium hydroxide and the like.

Among the compound (I) of this invention, the compound in which A ring has hydroxyamidino group or amidino group can be obtained using a compound in which the A ring in the compound (I) of this invention has nitrile group. This reaction is carried out in a solvent which is not involved in aforesaid reaction under cooling to warming. Moreover, depending on the applied process, there is a situation that the reaction proceeds smoothly by reacting in the presence of aforesaid base, or using these base as solvent.

As synthesis method of the compound in which A ring has amidino group, the methods shown in the following (i) to (iv) are nominated.

(i) Method in which nitrile is imidated, thereafter, it is condensed with amine:
Alcohol such as methanol, ethanol and the like is acted on a compound in which the A ring in the compound (I) of this invention has nitrile group in the presence of hydrochloric acid gas at -40 degrees to 0 degrees, thereby imidate is formed, thereafter, it is reacted with amine or amine salt such as ammonia, ammonium carbonate, ammonium chloride, ammonium acetate and the like. As solvent, a solvent which is not involved in aforesaid reaction can be used.

(ii) Method in which nitrile is converted to thioamide thereafter thioimidate is formed, and condensed with amine:
The compound in which the A ring in the compound (I) of this invention has nitrile group is reacted with hydrogen sulphide in the presence organic base such as methylamine, triethylamine, pyridine, picoline and the like, or the compound in which the A ring in the compound (I) of this invention has nitrile group is reacted with dithiophosphoric acid O,O-diethyl in the presence of hydrogen chloride, thereby thioamide body is obtained.

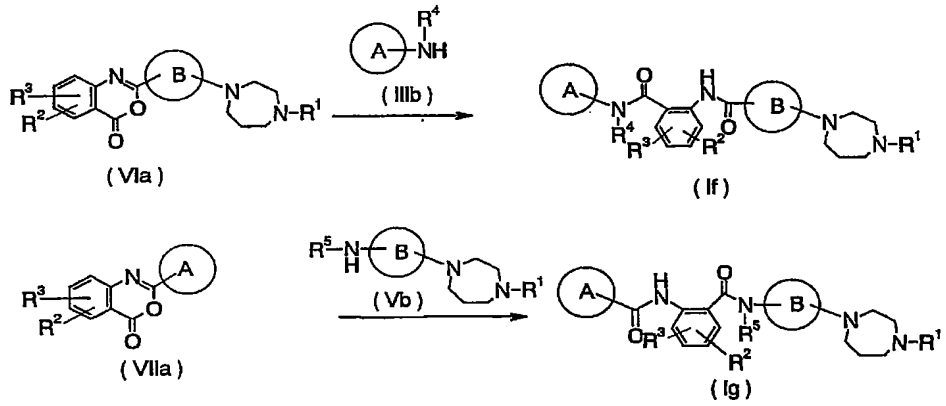
Next, lower alkyl halide such as methyl iodide, ethyl iodide and the like is reacted with aforesaid thioamide body, and thioimidate body is formed, thereafter, it is reacted with amine or amine salt such as ammonia, ammonium carbonate, ammonium chloride, ammonium acetate and the like. As solvent, a solvent which is not involved in aforesaid reaction can be used.

(iii) Method in which amine, amine salt, metal amide, Grignard reagent is directly added to the nitrile:
Reagent such as ammonia, ammonium chloride and ammonia, ammonium thiocyanate, alkylammonium thiocyanate, NaNH2, (CH)2NMgBr and the like is directly added to the compound in which the A ring in the compound (I) of this invention has nitrile group. As solvent, a solvent which is not involved in aforesaid reaction can be used. Or, the reaction can be carried out without solvent.

(iv) Method in which hydroxyamidino group is reduced:
Using the compound in which the A ring in the compound (I) of this invention has nitrile group, aforesaid hydrogenation reaction is carried out directly, or acetic acid or trifluoroacetic acid is acted using acetic acid, trifluoroacetic acid and the like as solvent, thereafter, aforesaid hydrogenation reaction is carried out, thereby hydroxyamidino group can be reduced.

Moreover, any method for the reaction for the formation of amidine group can be employed other than the method described here.

The compound represented by general formula (I) can be produced by arbitrary combination of the steps which can be adopted by person skilled in the art such as alkylation, acylation, oxidation, reduction, hydrolysis and the like. Moreover, the method shown in the following reaction equations is in particular effective for the synthesis of the compound represented by the general formula (I).

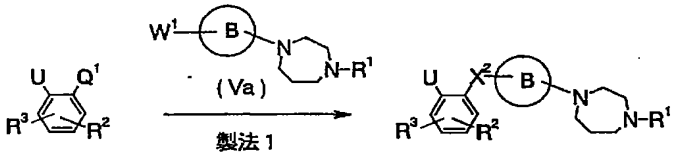


(wherein, A, B, R1, R2, R3, R4 and R5 have aforesaid meanings).

It is a reaction in which compound (VIa) and amine (IIIb) or compound (VIIa) and amine (Vb) are reacted thereby amide bond is formed and compound (If) or compound (Ig) is obtained, it is carried out in aforesaid inert solvent, at room temperature to warming. Moreover, depending on the applied process, there is a situation that the reaction proceeds smoothly by reacting in the presence of base such as N-methylmorpholine, triethylamine, trimethylamine, pyridine, sodium hydride, potassium-t-butoxide, butyllithium, sodium amide and the like or using these base as solvent.

(a production method of starting material compound)
Hereinafter, a typical process for the production of the starting material compound of the compound of this invention (I) is described.

Production method 1



(wherein, B, R1, R2, R8, Q1, W1 and X2 have aforesaid meanings, U denotes -COOH, -NHR5, -CH2-leaving group, -CHO, phosphonium slat such as -CH2-P[+]Ph3Br[-] and the like, phosphorous acid diester such as -CH2-P(=O)(-OEt)2 and the like, or phosphine oxide such as -CH2-P(=O)(-Ph)2 and the like. R5 has aforesaid meaning)

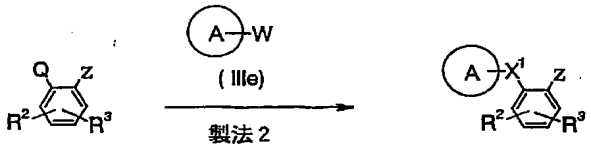
Production method 1

It is a reaction in which carboxylic acid and amine in a combination of compound (VIIIa) and compound (Va) are condensed, and amide bond is formed. This reaction is carried out in the same way as in aforesaid Step A.

Moreover, when U in compound (IIe) denotes -CH2-leaving group, the compound in which U is -CHO can be obtained by oxidation reaction using 4-methylmorpholine N-oxide and the like, and the compound in which U is phosphonium salt of for example -CH2-P[+]Ph3Br[-]can be obtained by reaction organophosphorous compound of for example triphenylphosphine and the like.

Moreover, the compound represented by general formula (IIe) can be produced by arbitrary combination of the steps which can be adopted by person skilled in the art such as alkylation, acylation, oxidation, reduction, hydrolysis and the like. For example, the compound having -NO2 at the site corresponding to U is obtained, thereafter aforesaid reduction reaction such as hudrogenation reaction is carried out, and the compound in which U is NH2 can be obtained. Moreover, the compound having ester group at the site corresponding to U is obtained, thereafter it is hydrolysed under acidic conditions using aqueous hydrochloric acid and the like or basic conditions using sodium hydroxide, and the compound in which U is -COOH can be obtained. Further, using the compound having amino group protected with t-butoxycarbonyl group or benzyl group, it is cleaved by the suitable process for cleaving each protecting group such as acidic conditions using trifluoroacetic acids and the like or reducing conditions of aforesaid hydrogenation, thereby the compound in which U is -NHR5 can be obtained.

Production method 2



(VIIIb)　　(IVb)

(wherein, A, R2, R3 and X1 have aforesaid meanings. Z denotes -COOH, -NHR5.
As for Q, W, when Q denotes Q1 then W denotes W1, and when Q denotes Q2 then W denotes -NHR4, and when Q denotes Q3 then W denotes -OH, and when Q denotes Q4, W denotes W4. Q1, Q2, Q3, Q4, W1, W4, R4 have aforesaid meanings.)

Production method 2.

When Q denotes Q1 and W denotes W1, it is a reaction in which carboxylic acid and the amine in a combination of compound (IIIe) and compound (VIIIb) are reacted and the compound (Ivb) is synthesised. This reaction can be carried out by the same process as step A.

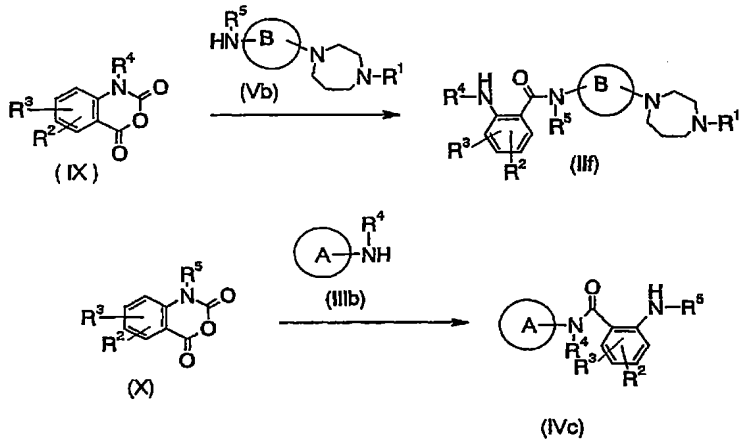
When Q denotes Q2 and W denotes -NHR4, it is a reaction in which aldehyde and amine or the compound having -CH2-leaving group and amine in a combination of compound (IIIe) and compound (VIIIb) are condensed, and the compound (IVb) is synthesised. This reaction can be carried out by the same process as step B.

When Q denotes Q3 and W denotes -OH, it is a reaction in which the compound having -CH2-leaving group and alcohol in a combination of compound (IIIe) and compound (VIIIb) are condensed, and the compound (IVb) is synthesised. This reaction can be carried out by the same process as step C.

When Q denotes Q4 and W denotes W4, it is a reaction in which aldehyde and phosphonium salt, phosphorous acid diester or the phosphine oxide in a combination of compound (IIIe) and compound (VIIIb) are condensed, and the compound (IVb) is synthesised. This reaction can be carried out by the same process as step D.

Moreover, the compound represented by general formula (IVb) can be produced by arbitrary combination of the steps which can be adopted by person skilled in the art such as alkylation, acylation, oxidation, reduction, hydrolysis and the like. For example, a compound having -NO2 at the site corresponding to Z is obtained, thereafter the compound in which Z is -NH2 can be obtained by reduction reaction such as aforesaid hydrogenation reaction. Moreover, the compound having ester group at the site corresponding to Z is obtained, thereafter it is hydrolysed under acidic conditions using aqueous hydrochloric acid of basic conditions using sodium hydroxide and the like, and the compound in which Z is -COOH can be obtained. Further, using the compound having amino group protected with t-butoxycarbonyl group or benzyl group at the site corresponding to Z, it is cleaved by the suitable process for cleaving each protecting group such as acidic conditions using trifluoroacetic acids and the like or reducing conditions of aforesaid hydrogenation, thereby the compound in which Z is -NHR5 can be obtained.

Moreover, the process shown in the following reaction equation is in particular effective for the synthesis of the compound represented by general formula (IIf), (IVc).



(wherein, A, B, R1, R2, R3, R4 and R5 have aforesaid meanings).

It is a reaction in which compound (IX) and amine (Vb) or compound (X) and amine (IIIb) are reacted thereby amide bond is formed and compound (IIf) or compound (IVc) is obtained, it is carried out in aforesaid inert solvent, at room temperature to warming. Moreover, depending on the applied process, there is a situation that the reaction proceeds smoothly by reacting in the presence of base such as N-methylmorpholine, triethylamine, trimethylamine, pyridine, sodium hydride, potassium-t-butoxide, butyllithium, sodium amide and the like or using these base as solvent.

The compound of this invention produced in this way can be isolated and refined by using well known method such as extraction, sedimentation, fraction chromatography, fractional crystallisation, recrystallisation and the like. Moreover, as salt of the compound of this invention, desired salt can be derived by subjecting to ordinary salt formation reaction.

Moreover, when the compounds of this invention have asymmetric carbon, optical isomer is present. These optical isomers can be separated by conventional procedures such as fractional crystallisation by recrystallisation with appropriate salt or column chromatography and the like.

Possible applications in industry

The compound of this invention inhibits activated blood coagulating factor X specifically and has a strong anticoagulation action. Accordingly it is useful as a blood clotting inhibitor or a prevention • therapeutic agent of disease caused by thrombosis or embolus.

As aforesaid diseases, diseases caused by cerebral blood vessel damage such as cerebral infarction, cerebral thrombosis, cerebral embolism, transient ischemic attack (TIA), subarachnoid bleeding (angiospasm), ischemic cardiac diseases such as acute and chronic myocardial infarction, unstable angina, coronary artery thrombolysis, diseases caused by lung angiopathy such as pulmonary infarction, lung embolus, furthermore, periphery artery thrombosis, deep vein thrombosis, disseminated intravascular coagulation syndrome, thrombogenesis after artificial blood vessel or synthetic valve implantation, reocclusion and restenosis after coronary artery bypass operation, reocclusion and restenosis after PTCA (Percutaneous transluminal coronary angioplasty), PTCR (Percutaneous transluminal coronary recanalisation) operation, thrombogenesis during extracorporeal circulation or the like are nominated.

Moreover, because the possibility as infection prevention • therapeutic agent of influenza virus on the basis of proliferation inhibiting activity of influenza virus is suggested (Kokai 6-227971) for the compound having activated blood coagulating factor X inhibitory effect, the same effect is expected in the compound of this invention

The excellent activated blood coagulating factor X inhibiting activity of the compound of this invention was confirmed by the following tests.

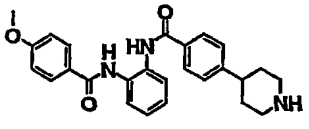
1) Human activated blood coagulating factor X (human factor Xa) coagulation time measurement.
The agent or physiological saline 10 μl and human factor Xa (Enzyme Research Labs) 50 μl were added to human plasma 90 μl, and it was incubated at 37 degrees for three minutes, and thereafter, 20 mM of CaCl2 100 μl which was warmed to 37 degrees beforehand was added and coagulation time was measured by coagulation meter (Amelung company: KC10). Human plasma was collected from elbow vein of healthy subjects (6 people) by 45 ml using a syringe containing 5 ml of 3.8 % sodium citrate, and the plasma which was separated by centrifugation at 4 degrees /3000 rpm /15 minutes was pooled, cryopreserved and used. Human factor Xa was selected at a concentration in which the coagulation time when physiological saline (control) was added became about 30-40 seconds. The CT2 value (concentration to prolong the coagulation time of control by twice) was determined by plotting the relative value of coagulation time with respect to control (fold) and drug concentration, and by linear regression. The results are shown in the following Table 1.

2) Bovine thrombin coagulation time measurement.
The agent or physiological saline 50 μl was added to human plasma 50 μl, and it was incubated at 37 degrees for three minutes, and thereafter thrombin 50 μl warmed to 37 degrees beforehand was

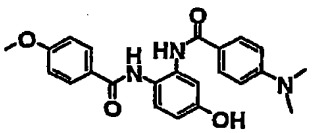
added, and coagulation time was measured by coagulation meter (Amelung company: KC10). Human plasma was collected from elbow vein of healthy subjects (6 people) by 45 ml using a syringe containing 5 ml of 3.8 % sodium citrate, and the plasma which was separated by centrifugation at 4 degrees /3000 rpm /15 minutes was pooled, cryopreserved and used. Thrombin was selected at a concentration in which the coagulation time when physiological saline (control) was added became about 20 seconds. The CT2 value (concentration to prolong the coagulation time of control by twice) was determined by plotting the relative value of coagulation time with respect to control (fold) and drug concentration, and by linear regression. The results are shown in the following Table 1.

Table 1.

	Compound	Human activated blood coagulating factor X coagulation time (CT2) (μM)	Bovine thrombin coagulation time (CT2) (μM)
Example compound	Example 5	0.10	>100
	Example 9	1.71	>100
	Example 11	1.33	>100
	Example 32	1.41	>100
	Example 39	1.53	>100
Control compound	Control 1	17.0	>100
	Control 2	11.3	–



(Control 1)
(Example 42 of WO 99/00121)



(Control 2)
(Example 198 of WO 99/00121)

3) Enzyme inhibition measurement test by synthetic substrate method.

Reaction buffer (pH 8.4) 80 μl, compound solution 15 μl, synthetic substrate S-2222 (Chromogenix) 2 mM 30 μl were added to 96 well microplate, and human activated blood coagulating factor X (factor Xa Enzyme Research Labs) 0.025 U/ml 25 μl was added and it was reacted at 37 degrees for ten minutes, and thereafter absorbance change at 405 nm was measured with Bio-Rad Company model 3550, and IC50 was calculated. The compound of Example 1 showed IC50 of less than 10 nM or less.

From the results of the measurement of above 1), 2) and 3), it was confirmed that the compound of this invention specifically inhibited human activated blood coagulating factor X and also showed strong anti blood clotting action. For example, the compounds shown in Examples 5, 9, 11, 32 and 39 of this invention prolonged the coagulation time clearly at a lower concentration compared with Example 42 of WO99/00121 (control 1) and same Example 198 (control 2), and it excellent anti blood clotting action was confirmed.

4) ex vivo coagulation time measurement using mouse (oral administration).

The drug dissolved or suspended in 0.5 % methyl cellulose was forcibly orally-administered (10 mg/kg), using oral tube to male ICR mice which was fasted for 12 hours or more (20-30 g, Japan SLC company), and at 30 minutes and two hours later the blood 0.9 ml was collected using the syringe containing 100 μl of 3.8 % sodium citrate from inferior vena cava under diethyl ether anaesthesia , and the plasma was separated by centrifugation at 3000 rpm /10 minutes. Using this plasma, extrinsic system coagulation time (PT) and intrinsinc system coagulation time (APTT) were measured in accordance with the method of the following a) and b).

a) Extrinsic system coagulation time (PT).

Ortho brain thromboplastin (54 mg/vial, freeze-dried preparation, Ortho clinical diagnostics company) was dissolved in Milli-Q water 2.5 ml, and it was preliminary warmed at 37 degrees. Aforesaid plasma 50 μl was warmed to 37 degrees for one minute, and aforesaid thromboplastin solution 50 μl was added, and measurement of coagulation time was carried out. Amelung company KC10A was used for the measurement of coagulation time.

b) Intrinsinc system coagulation time (APTT).

Hemoliance thrombosil I (diayatron company) 50 μl was added to aforesaid plasma 50 μl, and it was warmed to 37 degrees for three minutes, and 50 μl of 20 mM CaCl2 solution preliminary warmed to 37 degrees beforehand was added, and measurement of coagulation time was carried out. Amelung company KC10A was used for the measurement of coagulation time.

Moreover administration dosage or collection of blood time was changed, and dose dependency and change with time of anticoagulation product, was investigated by the same process.

5) ex vivo coagulation time measurement using cynomolgus monkey (oral administration).

After the blood collection before the drug administration, the drug (5 mg/ml) dissolved (suspension) in 0.5 % methyl cellulose was forcibly orally-administered by 2 ml/kg using oral tube to the male

cynomolgus monkey which was fasted for 12 hours or more (around 4 kg in weight) and 1, 2, 4, 6, 8 hours later, blood was collected by 2 ml with 3.8 % sodium citrate 1/10 vol. from femoral vein, the plasma was separated by centrifugation at 3000 rpm /10 minutes. Using this plasma, extrinsic system coagulation time (PT) and intrinsinc system coagulation time (APTT) were measured in accordance with the method of aforesaid a) and b). The test was carried out under un-anaesthetised conditions.

As a result of 4) and 5), as for the compound of this invention, prolongation action of coagulation time was observed in oral administration. The compound shown in Example 3 showed coagulation time prolongation action of twice or more in both PT, APTT in both tests of 4) and 5) compared to the control (plasma before drug administration).

The medicinal composition containing as effective ingredient at least one of the compound of this invention represented by the general formula (I) and the pharmaceutically acceptable salt thereof is prepared using a carrier and excipient usually used for formulation, other additives into a tablet, powder, fine granules, granules, capsule agent, pill, liquid agent, injection, suppository, ointment, patch, and is administered aorally or orally.

Clinical dosage with respect to human of the compound of this invention is suitably determined on consideration of the symptoms, body weight, age or gender of the patient, but it is 0.1-500 mg for oral administration and 0.01-100 mg for aoral administration, and this is administered once or divided into several times usually per adult per day. Because the dosage changes under various conditions, there is a case that a smaller quantity than aforesaid dosage range is adequate.

As solid composition for oral administration in accordance with this invention, tablet, powder, granule and the like are used. In such solid composition, at least one active material is mixed with at least one inert diluent, for example lactose, mannitol, dextrose, hydroxypropylcellulose, microcrystalline cellulose, starch, polyvinylpyrrolidone, metasilicate, magnesium aluminate. In accordance with normal methods, the composition may contain additives other than inert diluents, for example lubricant such as magnesium stearate and disintegrating agent such as calcium carboxymethyl cellulose, stabilising agent such as lactose, solubiliser or solubilising agent such as glutamic acid or aspartic acid. A tablet or pill may be film coated in accordance with requirement with sucrose, film of intestine soluble or stomach soluble substance such as gelatin, hydroxypropylcellulose, hydroxypropyl methyl cellulose phthalate.

Liquid composition for oral administration includes pharmaceutically acceptable opacifier, solvent, suspending agent, syrup, elixir agent and the like, and generally used inert diluent, for example purified water, ethanol are included. This composition may contain solubilising agent, solubiliser, wetting agent, adjuvant such as suspending agent, sweetener, flavour agent, aromatic and preservatives besides inert diluent.

As injection agent for aoral administration, sterile aqueous or non-aqueous solvent, suspending agent, opacifier are included. As diluent of aqueous solvent and suspending agent, for example distilled water for injection and physiological saline are included. As diluent of water insoluble solvent and suspending agent, there are for example propylene glycol polyethyleneglycol, vegetable oil such as olive oil, an alcohol such as ethanol, polysorbate 80 (Trade name) and the like.

Furthermore, such composition may include isotonisation agent, preservatives, wetting agent, emulsifier, dispersant, stabilising agent (for example lactose), additive such as solubilising agent or solubiliser. These are sterilised by for example filtration through bacteria retaining filter, formulation of fungicide or irradiation. These and produced as sterile solid composition and dissolved in sterile water or the sterile injectable solvent before use and can be used.

Ideal form for Carrying Out the Invention

Hereinafter, Production Example of the compound of this invention is nominated, and a process for the production of the compound of this invention is described in concrete terms. Moreover the novel compound is contained starting material compound of the compound of this invention, too, and a process for the production of the compound of these is described as Reference Example.

Reference Example 1.

Ethyl 4-bromomethyl-3-nitrobenzoate 26.00 g were dissolved in acetonitrile 90 ml, and 3-aminobenzo nitrile 7.97 g and potassium carbonate 12.44 g were added and the mixture stirred at 70 degrees for three hours. The mixture was cooled to room temperature, and, after filtration, mother liquor was concentrated under reduced pressure. Acetic acid ethyl ester was added to the obtained residue, and it was washed with 1 N aqueous hydrochloric acid, saturated aqueous sodium bicarbonate solution, and thereafter dried with anhydrous magnesium sulphate, and next it was concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography with hexane : ethyl acetate (80:20 to 75:25) as elution solvent, and ethyl 4-[(3-cyanophenylamino) methyl]-3-nitrobenzoate 12.06 g was obtained.

Reference Example 2.

Ethyl 4-[(3-cyanophenyl amino) methyl]-3-nitrobenzoate 5.79 g was dissolved in ethanol 50 ml, and purified water 50 ml, ammonium chloride 0.96 g, iron powder 4.97 g were added, and the mixture was heated under reflux for 40 minutes. The reaction liquor was filtered with celite, and it was concentrated under reduced pressure. Acetic acid ethyl ester was added to the obtained residue, and the mixture was washed with saturated aqueous sodium bicarbonate solution and saturated aqueous sodium chloride solution, dried with anhydrous magnesium sulphate, and next it was concentrated under reduced pressure, dried, and thereby ethyl 3-amino-4-[(3-cyanophenyl amino) methyl] benzoate 5.71 g was obtained.

Reference Example 3.

Ethyl 4-bromomethyl-3-nitrobenzoate 46.11 g was dissolved in acetonitrile 50 ml and 4-methylmorpholine-N-oxide 20 g was added to this and the mixture was stirred at room temperature for 80 minutes. The reaction liquor was concentrated under vacuum and water was added and it was extracted with chloroform. This organic layer was washed with saturated aqueous sodium chloride solution, and after drying with magnesium sulphate, it was concentrated under vacuum. The obtained residue was purified by silica gel column chromatography hexane : ethyl acetate (4:1), and ethyl 4-formyl-3-nitrobenzoate 10.723 g was obtained.

Reference Example 4.

Ethyl 4-formyl-3-nitrobenzoate 5.81 g was dissolved in toluene 7 ml, and 1,8-diazabicyclo [5.4.0]-undec-7-ene 2.1 ml was added to this and the mixture was stirred at 80 degrees for one hour. 3-[(1,1,1-triphenylphosphonio(?)) methyl] benzonitrile bromide 2.69 g was added to this and the mixture was stirred at 80 degrees for 24 hours. The insolubles were filtered, and the filtrate was concentrated under vacuum. The obtained residue was purified by silica gel column chromatography with hexane : ethyl acetate (10:1) as elution solvent. The obtained intermediate 3.1 g was dissolved in mixed solvent of ethanol 5 ml and tetrahydrofuran 10 ml, and palladium oxide barium sulphate complex 1 g was added to this and the mixture was stirred at room temperature under hydrogen atmosphere for three days. The reaction liquor was filtered with celite, and thereafter the filtrate was concentrated under vacuum. The obtained residue was purified by silica gel column chromatography hexane : ethyl acetate (2:1), and ethyl 3-amino-4-[2-(3-cyanophenyl) ethyl] benzoate 2.35 g was obtained.

Reference Example 5.

3-hydroxy-2-nitro benzoic acid 1.83 g was dissolved in N,N-dimethylformamide 50 ml and 4-methoxyaniline 1.23 g, 1-ethyl-3-dimethylaminopropyl carbodiimide hydrochloride 2.50 g, 1-hydroxybenzotriazole 1.35 g and triethylamine 1.81 ml were added to this and the mixture was stirred at room temperature for 66 hours. The reaction liquor was concentrated under vacuum, and water was added and it was extracted with acetic acid ethyl ester. This organic layer was washed with saturated aqueous sodium chloride solution, and after drying with magnesium sulphate it was concentrated under vacuum. Chloroform was added to the obtained residue, and produced sedimentation was recovered by filtration, and 3-hydroxy-4'-methoxy-2-nitro benzanilide 2.04 g was obtained. The filtrate was purified by silica gel column chromatography with chloroform : methanol (98:2) as elution solvent, and furthermore, chloroform was added to the obtained crude product, and produced sedimentation was recovered by filtration, thereby 3-hydroxy-4'-methoxy-2-nitrobenzanilide 0.24 g was obtained.

Reference Example 6.

3-hydroxy-4'-methoxy-2-nitrobenzanilide 1.15 g was suspended in methanol 50 ml and 10 % palladium-carbon powder 300 mg was added and the mixture was stirred at room temperature under hydrogen atmosphere for one hour. The reaction liquor was filtered with celite and was washed with methanol, and next the filtrate was concentrated under reduced pressure, and 2-amino-3-hydroxy-4'-methoxybenzanilide 966 mg was obtained.

Reference Example 7.

4-(4-methyl-1,4-diazepan-1-yl) benzonitrile 18.86 g was dissolved in 12 N hydrochloric acid 185 ml and the mixture was stirred at 80 degrees for 12 hours, and thereafter it was concentrated under vacuum. Water was added, the mixture was stirred at room temperature, thereafter formed sedimentation was filtered, and it was washed with water. The obtained solid was dried under reduced pressure, and 4-(4-methyl-1,4-diazepan-1-yl) benzoic acid hydrochloride 18.25 g was obtained.

Reference Example 8.

A mixture of 4-(4-methyl-1,4-diazepan-1-yl) benzoic acid hydrochloride 16.3 g, N,N-dimethylformamide 0.88 g, thionyl chloride 14.3 g and ethyl acetate 160 mL was stirred at 40 degrees for three hours and thereafter concentrated under vacuum. A solution of 2-amino-3-nitrophenol 8.35 g, pyridine 9.52 g and acetonitrile 60 mL was added under ice cooling to a mixture of the obtained residue and acetonitrile 130 ml. The mixture was stirred at 5 degrees or less overnight, and thereafter the crystals were recovered by filtration, and 2-amino-3-nitrophenyl 4-(4-methyl-1,4-diazepan-1-yl) benzoate hydrochloride 21.4 g was obtained.

Reference Example 9.

A mixture of 2-amino-3-nitrophenyl 4-(4-methyl-1,4-diazepan-1-yl) benzoate hydrochloride 2.00 g, triethylamine 995 mg and acetonitrile 20 mL was stirred at 70 degrees for 6 hours. A solution of sodium hydroxide 197 mg and water 2 mL was added to the reaction liquor. Water 20 mL was added, thereafter acetonitrile was eliminated by heating and distillation at ambient pressure, and furthermore water 10 mL was added, and the mixture was stirred at room temperature for 14 hours. The precipitated crystals were recovered by filtration, and 2'-hydroxy-4-(4-methyl-1,4-diazepan-1-yl)-6'-nitro benzanilide 1.57 g was obtained.

Reference Example 10.

A mixture of 2'-hydroxy-4-(4-methyl-1,4-diazepan-1-yl)-6'-nitro benzanilide 2.14 g, methanol 43 mL and 10 % palladium-carbon (wet rate 54.2 %) 467 mg was stirred under hydrogen atmosphere at ambient pressure at 30 degrees, till absorption of hydrogen stopped. The catalyst was eliminated by filtration, and the filtrate was concentrated under vacuum. The residue was refined with silica gel chromatography (chloroform : methanol = 20:1 to 10:1), and 2'-amino-6'-hydroxy-4-(4-methyl-1,4-diazepan-1-yl) benzanilide 1.61 g were obtained.

Reference Example 11.

2-amino-3-nitrophenol 308 mg was dissolved in pyridine 10 ml, and 4-methoxybenzoyl chloride 341 mg was added at 0 degrees and the mixture was stirred at room temperature for 18 hours. The reaction liquor was concentrated under reduced pressure, chloroform 20 ml was added to the obtained residue, and it was concentrated under reduced pressure once again. Further this procedure was repeated three times, and the residue from which pyridine was eliminated, was purified by silica gel column chromatography with chloroform as elution solvent, and 2'-hydroxy-4-methoxy-6'-nitro benzanilide 428 mg was obtained. The compound of Reference Example 12 was synthesised in the same way as in Reference Example 6.

Reference Example 13.

3-hydroxy-2-nitro benzoic acid 10.5 g was dissolved in N,N-dimethylformamide 60 ml, and benzyl bromide 15 ml and potassium carbonate 19.0 g were added at 0 degrees, and the mixture was stirred at room temperature overnight. The reaction liquor was filtered with celite, and thereafter it was concentrated under reduced pressure. Water was added to the obtained residue, and it was extracted with ether, thereafter washed with saturated aqueous sodium chloride solution, and dried with anhydrous magnesium sulphate. The solvent was eliminated by distillation under reduced pressure, and benzyl 3-benzyloxy-2-nitrobenzoate 20.7 g was obtained.

Reference Example 14.

Ethanol 100 ml and 1N aqueous sodium hydroxide 120 ml were added to benzyl 3-benzyloxy-2-nitrobenzoate 20.7 g, and the mixture was stirred at room temperature overnight, at 60 degrees for three hours and at 80 degrees for five hours. Ethanol was eliminated by distillation under reduced pressure, and thereafter the obtained aqueous solution was washed with ether, and thereafter hydrochloric acid was added. Produced sedimentation was recovered by filtration, and thereafter it was dried under reduced pressure, and 3-benzyloxy-2-nitro benzoic acid 15.8 g was obtained.

Reference Example 15.

Thionyl chloride 20 ml and several drops of N,N-dimethylformamide were added to 3-benzyloxy-2-nitro benzoic acid 5.47 g, and the mixture was stirred at 80 degrees for 30 minutes. The reaction liquor was concentrated under reduced pressure, and pyridine 35 ml and 2-amino-5-chloropyridine 2.55 g were added to the obtained residue at 0 degrees, and the mixture was stirred at room temperature overnight. The reaction liquor was concentrated under reduced pressure, and saturated aqueous sodium bicarbonate solution was added to the obtained residue, and it was extracted with acetic acid ethyl ester. Organic layer was dried with anhydrous magnesium sulphate, the solvent was eliminated by distillation under reduced pressure, and azeotropic distillation with toluene was carried out, and 3-benzyloxy-N-(5-chloro-2-pyridyl)-2-nitrobenzamide 7.44 g was obtained.

Reference Example 16.

Trifluoroacetic acid 40 ml and pentamethylbenzene 3.72 g were added to 3-benzyloxy-N-(5-chloro-2-pyridyl)-2-nitrobenzamide 7.44 g and the mixture was stirred at 40 degrees overnight. The reaction liquor was concentrated under reduced pressure, and saturated aqueous sodium bicarbonate solution was added to the obtained residue by a degree that was not made alkaline, and it was extracted with acetic acid ethyl ester. The organic layer was extracted with 1N sodium hydroxide aqueous solution,

and thereafter hydrochloric acid was added to the aqueous layer, it was acidified, and it was extracted with chloroform. It was dried with anhydrous magnesium sulphate, next the solvent was eliminated by distillation under reduced pressure, ethanol suspension 200 ml of Raney nickel was added to the obtained residue. The mixture was stirred under hydrogen atmosphere for six hours, thereafter N,N-dimethylformamide was added, and the insolubles were eliminated by filtration. The solvent was eliminated under reduced pressure by distillation, and water was added to the obtained residue. The produced precipitate was recovered by filtration, dried under reduced pressure, and 2-amino-N-(5-chloro-2-pyridyl)-3-hydroxybenzamide 4.58 g was obtained.

Reference Example 17.

2-amino-N-(5-chloro-2-pyridyl)-3-hydroxybenzamide 3.06 g and N-chlorosuccinimide 1.80 g were dissolved in N,N-dimethylformamide 60 ml and the mixture was stirred at 50 degrees for eight hours and at room temperature for four hours, and thereafter the insolubles were eliminated by filtration. The solvent was eliminated under reduced pressure by distillation, and thereafter 1 N aqueous sodium hydroxide was added to the obtained residue, and it was extracted with acetic acid ethyl ester. The organic layer was dried with anhydrous magnesium sulphate, and next the solvent was eliminated by distillation under reduced pressure, and the obtained residue was refined using silica gel column chromatography. Ethanol was added to the obtained crude purified material, and produced precipitate was recovered by filtration, and it was dried under reduced pressure, and 2-amino-5-chloro-N-(5-chloro-2-pyridyl)-3-hydroxybenzamide 767 mg was obtained. Mother liquor was concentrated, ethyl acetate-isopropyl ether was added and the sedimentation produced was recovered by filtration, and thereafter it was dried under reduced pressure, thereby the aforesaid compound was further obtained by 942 mg.

The compounds of Reference Examples 18, 19 were synthesised in the same way as in Reference Example 17.

Reference Example 20.

Ethyl 2-amino-5-chloro-3-hydroxybenzoate 3.23 g was dissolved in 3 N hydrochloric acid solution 160 ml and the mixture was stirred at 85 degrees for three hours and at 80 degrees for five days. The reaction liquor was cooled to room temperature, and thereafter the insolubles were filtered, and 1N aqueous sodium hydroxide 320 ml was added to the filtrate, and the mixture was stirred at room temperature for one hour. The produced precipitate was filtered, and it was washed with purified water, thereafter dried under reduced pressure, and 2-amino-5-chloro-3-hydroxy benzoic acid 1.55 g was obtained.

Reference Example 21.

2-amino-5-chloro-3-hydroxy benzoic acid 1.12 g was dissolved in N,N-dimethylformamide 60 ml and 4-methoxyaniline 7.38 g, 1-ethyl-3-dimethylaminopropyl carbodiimide hydrochloride 1.73 g, 1-hydroxybenzotriazole 1.21 g and triethylamine 1.26 ml were added to this and the mixture was stirred at room temperature for 13 hours. The reaction liquor was concentrated under vacuum, and acetic acid ethyl ester was added to the obtained residue, and it was washed with purified water and saturated aqueous sodium chloride solution, dried with magnesium sulphate, and thereafter it was concentrated under reduced pressure. Chloroform was added to the obtained residue and the mixture was stirred for 30 minutes, and thereafter produced sedimentation was recovered by filtration, and it was washed with chloroform, thereafter dried under reduced pressure, and 2-amino-5-chloro-3-hydroxy-4'-methoxy-2-benzanilide 0.96 g was obtained.

Reference Example 22.

Thionyl chloride 40 ml was added to 4-(4-methyl-1,4-diazepan-1-yl) benzoic acid hydrochloride 5.09 g, and the mixture was stirred at 60 degrees for 30 minutes. The reaction liquor was concentrated under reduced pressure, and it was dried to a solid. A solution of ethyl 3-amino-4-[(3-cyanophenyl amino) methyl] benzoato 5.65 g dissolved in pyridine 50 ml was added to the obtained residue, and the mixture was stirred at room temperature for five hours. The reaction liquor was concentrated under reduced pressure, and thereafter acetic acid ethyl ester and chloroform were added to the obtained residue, and it was washed with saturated aqueous sodium bicarbonate solution and saturated aqueous sodium chloride solution, dried with anhydrous magnesium sulphate, and next concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography with hexane : ethyl acetate (95:5 to 90:10) as elution solvent, and ethyl 4-[(3-cyanophenyl amino) methyl]-3-[4-(4-methyl-1,4-diazepan-1-yl) benzoylamino] benzoate 6.42 g was obtained.

The compound of Reference Example 23 was synthesised in the same way as in Reference Example 22.

Example 1.

Ethyl 4-[(3-cyanophenyl amino) methyl]-3-[4-(4-methyl-1,4-diazepan-1-yl) benzoylamino] benzoate 4.09 g was dissolved in ethanol 80 ml, and hydrochloric acid gas was introduced at -20 degrees or less for 20 minutes, thereafter the mixture was warmed to 3 degrees and stirred for 24 hours. The reaction liquor was concentrated under reduced pressure, and dried to a solid, the obtained residue

was dissolved in ethanol 80 ml, and acetic acid ammonia 6.16 g was added and the mixture was stirred at room temperature for 3.5 days. The reaction liquor was concentrated under reduced pressure, the obtained residue was refined by ODS column chromatography with 0.002 N aqueous hydrochloric acid : ethanol (100:0 to 80:20) as elution solvent, thereafter it was freeze-dried, and ethyl 4-[(3-cyanophenyl amino) methyl]-3-[4-(4-methyl-1,4-diazepan-1-yl) benzoylamino] benzoate hydrochloride 3.84 g was obtained. Among the obtained compound, 1.70 g thereof was dissolved in ethanol 20 ml, and 1N aqueous sodium hydroxide 30 ml was added and, the mixture was stirred at room temperature for one hour. The reaction liquor was neutralised with 1 N aqueous hydrochloric acid, and thereafter it was concentrated under reduced pressure. The obtained residue was refined by ODS column chromatography with 0.002 N aqueous hydrochloric acid : acetonitrile (100:0 to 92:8) as elution solvent, and thereafter it was freeze-dried, and 4-[(3-carbamimidylphenyl amino methyl]-3-[4-(4-methyl-1,4-diazepan-1-yl) benzoylamino] benzoic acid hydrochloride 1.48 g was obtained.

Example 2.

Ethyl 4-[(3-cyanophenyl amino) methyl]-3-[4-(4-methyl-1,4-diazepan-1-yl) benzoylamino] benzoate 1.42 g was dissolved in ethanol 30 ml and hydroxylamine hydrochloride 291 mg and triethylamine 0.78 ml were added and the mixture was stirred at 60 degrees for 24 hours. The reaction liquor was concentrated under reduced pressure, the obtained residue was purified by silica gel column chromatography with chloroform : methanol : ammonia water solution (100:0:0 to 92:8:0.8) as elution solvent, and the crude purified material of ethyl 4-({[3-(N-hydroxycarbamimidyl) phenyl] amino} methyl)-3-[4-(4-methyl-1,4-diazepan-1-yl) benzoylamino] benzoate was obtained. Furthermore, it was refined by ODS column chromatography with 0.002 N aqueous hydrochloric acid : methanol (100:0 to 88:12) as elution solvent, thereafter it was freeze-dried, and ethyl 4-({[3-(N-hydroxycarbamimidyl) phenyl] amino} methyl)-3-[4-(4-methyl-1,4-diazepan-1-yl) benzoylamino] benzoato hydrochloride 1.03 g was obtained.

The compounds of Examples 3, 5, 7, 54 were synthesised in the same way as in Example 1.
The compounds of Examples 4, 6, 8, 53 were synthesised in the same way as in Example 2.

Example 9.

4-(4-methyl-1,4-diazepan-1-yl) benzoic acid hydrochloride 812 mg was dissolved in thionyl chloride 8 ml, and the mixture was stirred time at 60 degrees for 30 minutes. The reaction liquor was concentrated under reduced pressure, and it was dried to a solid. A solution of 2-amino-4'-methoxy-3-hydroxy benzanilide 774 mg dissolved in pyridine 15 ml was added to the obtained residue at 0 degrees and it was stirred at room temperature for two hours. The reaction liquor was concentrated

under reduced pressure, thereafter toluene was added to the obtained residue, and it was concentrated under reduced pressure once again. Saturated aqueous sodium bicarbonate solution and acetic acid ethyl ester were added to the obtained residue, and the obtained sedimentation was recovered by filtration. Ethyl acetate layer of the mother liquor was dried with anhydrous sodium sulphate, and thereafter it was concentrated under reduced pressure. The obtained residue and sedimentation recovered by filtration were mixed, and it was purified by silica gel column chromatography with chloroform : methanol (98:2) as elution solvent, and 3-hydroxy-4'-methoxy-2-{[4-(4-methyl-1,4-diazepan-1-yl) benzoyl] amino} benzanilide was obtained 873 mg. The obtained compound was suspended in ethanol 10 ml and 4 N hydrochloric acid ethyl acetate solution 0.7 ml was added and stirred, thereafter produced sedimentation was filtered, and it was washed with ethanol, and thereby 3-hydroxy-4'-methoxy-2-{[4-(4-methyl-1,4-diazepan-1-yl) benzoyl] amino} benzanilide hydrochloride 896 mg was obtained by drying under reduced pressure.

The compounds of Examples 10-16, 42, 51, 52 were synthesised in the same way as in Example 9.

Example 17.

2'-amino-6'-hydroxy-4-(4-methyl-1,4-diazepan-1-yl) benzanilide 2.03 g was dissolved in pyridine 60 ml, and 4-methoxybenzoyl chloride 1.12 g was added at 0 degrees and the mixture was stirred at room temperature for 3 days. The reaction liquor was concentrated under reduced pressure, and chloroform 150 ml was added to the obtained residue, and it was made alkaline using 5 % sodium hydrogen carbonate aqueous solution 150 ml, and it was extracted with chloroform. The obtained organic layer was dried with anhydrous sodium sulphate, thereafter it was concentrated under reduced pressure, toluene was added, and it was concentrated under reduced pressure once again. The obtained residue was purified by silica gel column chromatography with chloroform : methanol : saturated ammonia water (100:10:1) as elution solvent. It was recrystallised from ethanol, and 3-hydroxy-N1-(4-methoxybenzoyl)-N2-[4-(4-methyl-1,4-diazepan-1-yl) benzoyl]-1,2-phenylenediamine 1.74 g was obtained. 3-hydroxy-N1-(4-methoxybenzoyl)-N2-[4-(4-methyl-1,4-diazepan-1-yl) benzoyl]-1,2-phenylenediamine 1.10 g and maleic acid 269 mg were dissolved in 50 % ethanol aqueous solution 11 ml by heating, water 11 ml was added, and it was cooled, and the crystals produced were recovered by filtration, dried, and 3-hydroxy-N1-(4-methoxybenzoyl)-N2-[4-(4-methyl-1,4-diazepan-1-yl) benzoyl]-1,2-phenylenediamine maleate 1.18 g was obtained.

The compounds of Examples 18-35 were synthesised in the same way as in Example 17.

Example 36.

3-hydroxy-N1-(4-methoxybenzoyl)-N2-[4-(4-methyl-1,4-diazepan-1-yl) benzoyl]-1,2-phenylene diamine 500 mg was dissolved in methanol 11 ml, benzyl bromide 215 mg was added at room temperature and the mixture was stirred for five hours. Benzyl bromide 215 mg was added at room temperature, the mixture was stirred for 16 hours, and thereafter the precipitate was recovered by filtration. The obtained precipitate was suspended in N,N-dimethylformamide 11 ml, and bromoacetic acid ethyl ester 210 mg and potassium carbonate 174 mg were added at room temperature and the mixture was stirred at 100 degrees for 30 minutes. The insolubles were filtered, and it was concentrated under reduced pressure. The obtained residue was dissolved in acetic acid 16 ml, and 10 % palladium-carbon powder 100 mg was added, and the mixture was stirred under hydrogen atmosphere of 3 atmosphere, at room temperature for three hours. The reaction liquor was filtered with celite, washed with methanol, next the filtrate was concentrated under reduced pressure. Chloroform 50 ml was added to the obtained residue, and it was made alkaline using 5 % sodium hydrogen carbonate aqueous solution 50 ml, and it was extracted with chloroform. The obtained organic layer was dried with anhydrous sodium sulphate, and thereafter it was concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography with chloroform : methanol : saturated ammonia water (100:10:1) as elution solvent, and the crude purified material of ethyl (3-[(4-methoxybenzoyl) amino]-2-{[4-(4-methyl-1,4-diazepan-1-yl) benzoyl] amino} phenoxy) acetate 580 mg was obtained. The crude purified material thereof was refined with ODS column chromatography with 0.001 N hydrochloric acid : methanol (10:4) as elution solvent, and ethyl (3-[(4-methoxybenzoyl) amino]-2-{[4-(4-methyl-1,4-diazepan-1-yl) benzoyl] amino} phenoxy) acetate hydrochloride 350 mg was obtained.

Example 37.

Ethyl (3-[(4-methoxybenzoyl) amino]-2-{[4-(4-methyl-1,4-diazepan-1-yl) benzoyl] amino} phenoxy) acetate hydrochloride 350 mg was dissolved in methanol 6 ml and 1 N aqueous sodium hydroxide 1.8 ml was added at room temperature and the mixture was stirred for two hours. 1 N hydrochloric acid 1.8 ml was added, and it was concentrated under reduced pressure. The obtained residue was refined by ODS column chromatography with 0.001 N hydrochloric acid : acetonitrile (1:1) as elution solvent, and (3-[(4-methoxybenzoyl) amino]-2-{[4-(4-methyl-1,4-diazepan-1-yl) benzoyl] amino} phenoxy) acetic acid hydrochloride 254 mg was obtained.

The compound of Example 38 was synthesised in the same way as in Example 37.

Example 39.

Crude purified material 370 mg of ethyl (3-[(4-methoxybenzoyl) amino]-2-{[4-(4-methyl-1,4-diazepan-1-yl) benzoyl] amino} phenoxy) acetate was dissolved in tetrahydrofuran 7 ml, and sodium tetrahydro borate 108 mg was added at room temperature. A solution of methanol 930 mg dissolved in tetrahydrofuran 7 ml was dropwise added at 60 degrees over a period of 25 minutes. The mixture was stirred at 60 degrees for 2 hours. Water 1 ml was added at room temperature, and it was concentrated under reduced pressure. Aforesaid procedure was carried out with respect to the obtained residue once again, and thereafter the obtained residue was purified by silica gel column chromatography with chloroform : methanol : saturated ammonia water (100:10:1) as elution solvent. The obtained compound was suspended in ethanol 3 ml, and 1 N hydrochloric acid 0.4 ml was added, and it was concentrated under reduced pressure. Acetone 3 ml and distilled water 3 ml were added to the obtained residue, and produced sedimentation was filtered, and 3-(2-hydroxyethoxy)-N1-(4-methoxybenzoyl)-N2-[4-(4-methyl-1,4-diazepan-1-yl) benzoyl]-1,2-phenylenediamine hydrochloride 107 mg was obtained.

Example 40.

3-hydroxy-N1-(4-methoxybenzoyl)-N2-[4-(4H methyl-1,4-diazepan-1-yl) benzoyl]-1,2-phenylene diamine 730 mg was dissolved in tetrahydrofuran 20 ml, and methanol 0.13 ml, triphenyl phosphine 498 mg, diethyl azodicarboxylate 0.23 ml were added and the mixture was stirred at room temperature for 16.5 hours. The reaction liquor was concentrated under vacuum, thereafter the obtained residue was dissolved in chloroform, it was washed with 0.5 N aqueous sodium hydroxide and saturated aqueous sodium chloride solution, dried with anhydrous sodium sulphate, and thereafter concentrated under vacuum. The obtained residue was purified by silica gel column chromatography with chloroform : methanol (95:5 to 93:7) as elution solvent. The obtained crude purified material was dissolved in ethanol 10 ml, 4 N hydrochloric acid ethyl acetate solution 0.4 ml was added, and thereafter it was concentrated under vacuum. The obtained residue was refined by ODS column chromatography with 0.002 N aqueous hydrochloric acid : acetonitrile (97:3 to 85:15), thereafter it was freeze-dried, and 3-methoxy-N1-(4-methoxybenzoyl)-N2-[4-(4-methyl-1,4-diazepan-1-yl) benzoyl]-1,2-phenylenediamine hydrochloride 335 mg was obtained.

Example 41.

3-hydroxy-N1-(4-methoxybenzoyl)-N2-[4-(4-methyl-1,4-diazepan-1-yl) benzoyl]-1,2-phenylene diamine 474 mg was dissolved in N,N-dimethylformamide 15 ml, trimethylamine-sulphur trioxide complex 1.39 g was added and the mixture was stirred at 60 degrees for 79 hours. Furthermore, trimethylamine-sulphur trioxide complex 0.42 g was added, the mixture was stirred at 60 degrees for 38 hours and furthermore, trimethylamine-sulphur trioxide complex 0.42 g was added and the

mixture was stirred at 60 degrees for 23 hours, and thereafter it was concentrated under vacuum. Water was added to the obtained residue, and the mixture was stirred for one hour, thereafter produced sedimentation was recovered by filtration, and it was washed with water. The obtained crude purified material was suspended in ethanol, after stirring, it was filtered, and it was washed with ethanol and water, thereafter it was dried under reduced pressure, and 3-[(4-methoxybenzoyl amino]-2-{[4-(4-methyl-1,4-diazepan-1-yl) benzoyl] amino} phenyl hydrogen sulphate 483 mg was obtained.

Example 43.

N2-[4-(4-benzyl-1,4-diazepan-1-yl) benzoyl]-3-hydroxy-N1-(4-methoxybenzoyl)-1,2-phenylene diamine 11.53 g was dissolved in acetic acid 250 ml, and 10 % palladium-carbon powder 2.5 g was added and, the mixture was stirred under hydrogen atmosphere of 3 atmosphere at room temperature for 44 hours. The reaction liquor was filtered with celite, washed with acetic acid, and next the filtrate was concentrated under vacuum. Toluene was added, it was concentrated under vacuum again, and the residue 11.11 g was obtained. Among the residues, 2.00 g thereof was dissolved in a mixed solvent of chloroform, aqueous sodium hydrogen carbonate, methanol and the mixture was stirred for 12 hours. After separation, the organic layer was washed with saturated aqueous sodium chloride solution, it was dried with anhydrous sodium sulphate and concentrated under vacuum. The obtained residue was suspended in ethanol, it was stirred for three hours, thereafter precipitate was filtered, and it was washed with ethanol. The obtained solid was recrystallised from ethanol, and N2-[4-(1,4-diazepan-1-yl) benzoyl]-3-hydroxy-N1-(4-methoxybenzoyl)-1,2-phenylenediamine was obtained. Furthermore it was crystallised from 0.5 N HCI, and N2-[4-(1,4-diazepan-1-yl) benzoyl]-3-hydroxy-N1-(4-methoxybenzoyl)-1,2-phenylene diamine hydrochloride 878 mg was obtained.

Example 44.

3-hydroxy-N1-(4-methoxybenzoyl)-N2-[4-(1,4-diazepan-1-yl) benzoyl]-1,2-phenylenediamine 857 mg was suspended in dichloromethane 20 ml, and acetic acid 1.2 g and cyclopropane carbaldehyde 261 mg and triacetoxy borohydride 789 mg were added at room temperature. The mixture was stirred for two hours, thereafter cyclopropane carbaldehyde 261 mg and triacetoxy borohydride 789 mg were added at room temperature and furthermore the mixture was stirred for two hours. The reaction liquor was concentrated under reduced pressure, and thereafter chloroform 50 ml was added to the obtained residue, and it was made alkaline using 5 % sodium hydrogen carbonate aqueous solution 50 ml, and it was extracted with chloroform. The obtained organic layer was dried with anhydrous sodium sulphate, and thereafter it was concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography with chloroform : methanol : saturated ammonia

water (100:10:1). The obtained compound was suspended in ethanol 13 ml, and 1 N hydrochloric acid 1.9 ml was added, and produced sedimentation was filtered, and 3-hydroxy-N1-(4-methoxybenzoyl)-N2-[4-(4-cyclopropylmethyl-1,4-diazepan-1-yl) benzoyl]-1,2-phenylenediamine hydrochloride 656 mg was obtained.

Example 45.

N2-[4-(1,4-diazepan-1-yl) benzoyl]-3-hydroxy-N1-(4-methoxybenzoyl)-1,2-phenylenediamine 1.3 g was dissolved in ethanol 20 ml, ethyl aceto imidate hydrochloride 1.04 g and triethylamine 1.5 ml were added and the mixture was stirred for 17 hours. Furthermore, ethanol 150 ml, ethyl acetimidate hydrochloride 1.04 g, triethylamine 1.5 ml were added and the mixture was stirred at 50 degrees for 68 hours. The reaction liquor was concentrated under vacuum, and the obtained residue was refined by ODS column chromatography with 0.002 N hydrochloric acid solution : acetonitrile (95:5 to 70:30), thereafter it was freeze-dried, and 3-hydroxy-N2-{4-[4-(1-iminoethyl)-1,4-diazepan-1-yl] benzoyl)-N1-(4-methoxybenzoyl)-1,2-phenylenediamine hydrochloride 515 mg was obtained.

The compounds of Examples 46-48 were synthesised in the same way as in Example 44.

Example 49.

4-(4-methyl-1,4-diazepan-1-yl) benzoic acid hydrochloride 755 mg was dissolved in thionyl chloride 2.2 ml, and the mixture was stirred at 60 degrees for 30 minutes. The reaction liquor was concentrated under reduced pressure, and it was dried to a solid. A solution of 2-amino-5-chloro-N-(5-chloro-2-pyridyl)-3-hydroxybenzamide 891 mg dissolved in pyridine 10 ml was added to the obtained residue, and the mixture was stirred at room temperature for 13 hours. The reaction liquor was concentrated under reduced pressure, thereafter acetic acid 20 ml was added to the obtained residue and the mixture was stirred at room temperature for 17 hours. The reaction liquor was concentrated under reduced pressure, thereafter saturated aqueous sodium bicarbonate solution was added to the obtained residue, it was extracted with chloroform, dried with anhydrous sodium sulphate, and thereafter concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography with chloroform : methanol : ammonia water (97:3:0.3 to 95:5:0.5), and the crude purified material of 5-chloro-N-(5-chloro-2-pyridyl)-3-hydroxy-2-([4-(4-methyl-1,4-diazepan-1-yl) benzoyl] amino} benzamide was obtained. Furthermore, this was refined by ODS column chromatography with acetonitrile : 0.002 N aqueous hydrochloric acid (2:8 to 3:7) as elution solvent, and it was suspended in dilute aqueous hydrochloric acid, freeze-dried, and 5-chloro-N-(5-chloro-2-pyridyl)-3-hydroxy-2-{[4-(4-methyl-1,4-diazepan-1-yl) benzoyl] amino} benzamide hydrochloride 492 mg was obtained.

The compound of Example 50 was synthesised in the same way as in Example 49.

Structural formulae and physico-chemical characteristics of the aforesaid Reference Example compounds and Example compounds are shown in separate Tables 2 and 3. The compounds shown in Tables 4-6 can be easily synthesised by almost the same process of aforesaid Example or the production method, or applying some modifications which are self-evident to a person skilled in the art. Moreover the symbols in the Table have following meanings.

Rf: Reference Example number, Ex: Example number, structure: structural formula, salt: salt, free: free body, DATA: physical properties data, NMR: nuclear magnetic resonance spectrum (TMS internal standard), FAB-MS: mass spectrometry value, Me: methyl, Et: ethyl.

表2

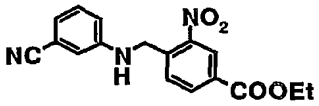
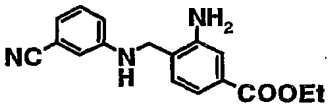
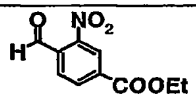
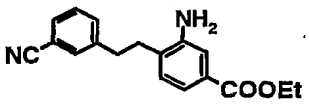
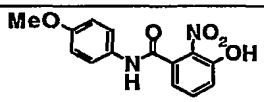
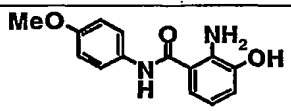
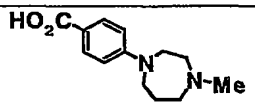
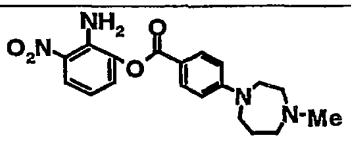
Rf	structure(salt)	DATA
1	 (free)	NMR($CDCl_3$): δ:1.42(3H, t, J = 7.2 Hz), 4.43(2H, q, J = 7.2Hz), 4.63(1H, t, J = 5.7 Hz), 4.81(2H, d, J = 6.0 Hz), 6.72 - 6.78(2H, m), 7.01(1H, dt, J = 1.3 Hz, 7.7 Hz), 7.19 - 7.27(1H, m), 7.69(1H, d, J = 8.1 Hz), 8.24(1H, dd, J = 1.7 Hz, 8.0 Hz), 8.73(1H, d, J = 1.7 Hz)
2	 (free)	NMR($CDCl_3$): δ:1.39(3H, t, J = 7.1 Hz), 3.96 - 4.16(3H, m), 4.25(2H, d, J = 4.2 Hz), 4.36(2H, q, J = 7.1Hz), 6.85 - 6.93(2H, m), 7.05(1H, dt, J = 1.2 Hz, 7.9 Hz), 7.22(1H, d, J = 7.7 Hz), 7.27(1H, t, J = 8.0 Hz), 7.41(1H, d, J = 1.3 Hz), 7.43(1H, dd, J = 1.7 Hz, 7.7 Hz)
3	 (free)	NMR($CDCl_3$): δ: 1.46(3H, t, J=7.2Hz), 4.48(2H, q, J=7.2Hz), 8.00(1H, d, J=8.0Hz), 8.42(1H, d, J=8.0Hz), 8.75(1H, s), 10.46(1H, s)
4	 (free)	NMR($CDCl_3$): δ: 1.38(3H, t, J=7.1Hz), 2.82(2H, t, J=8.4Hz), 2.96(2H, t, J=8.4Hz), 4.34(2H, q, J=7.1Hz), 6.97(1H, d, J=8.4Hz), 7.33-7.41(4H, m), 7.44-7.52(2H, m)
5	 (free)	NMR(DMSO-d_6): δ: 3.74(3H, s), 6.92(2H, d, J = 8.8 Hz), 7.19 - 7.30(2H, m), 7.50(1H, t, J = 8.6 Hz), 7.58(2H, d, J = 9.3 Hz), 10.46(1H, s), 11.25(1H, brs),
6	 (free)	NMR(DMSO-d_6): δ: 3.74(3H, s), 5.79(2H, s), 6.46(1H, t, J = 7.8 Hz), 6.82(1H, d, J = 7.8 Hz), 6.90(2H, d, J = 8.8 Hz), 7.15(1H, d, J = 7.8 Hz), 7.61(2H, d, J = 8.8 Hz), 9.56(1H, s), 9.81(1H, s),
7	 HCl	NMR(DMSO-d_6): δ:2.06 - 2.24(1H, m), 2.30 - 2.45(1H, m), 2.77(3H, s), 3.00 - 3.24(2H, m), 3.24 - 3.55(4H, m), 3.70 - 4.00(2H, m), 6.81(2H, d, J = 9.1 Hz), 7.78(2H, d, J = 9.1 Hz), 11.06(1H, s), 12.20(1H, s)
8	 HCl	NMR(DMSO-d_6) δ:2.15 - 2.22(1H, m), 2.34-2.45(1H, m), 2.79(3H, d, J = 5.0Hz), 3.05 - 3.22(2H, m), 3.40 - 3.61(4H, m), 3.79 - 3.88(1H, m), 3.95 - 4.03(1H, m), 6.69 - 6.75(1H, m), 6.93(2H, d, J = 9.0 Hz), 7.05(2H, br), 8.00(2H, d, J = 9.0 Hz), 11.12(1H, br)

表２（続き）

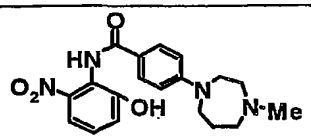
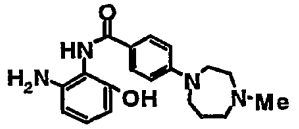
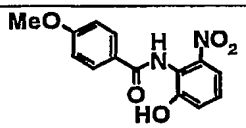
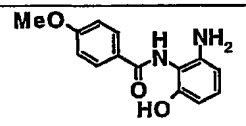
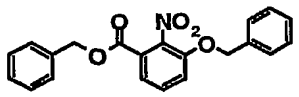
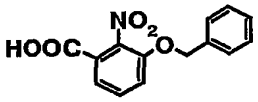
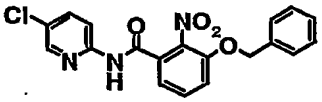
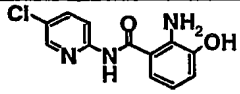
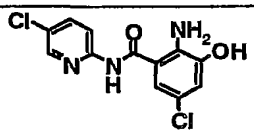
9	 (free)	NMR(DMSO-d_6) δ:1.86-1.95(2H, m), 2.29(3H, s), 2.45 - 2.52(2H, m), 2.65(2H, t, J = 4.4Hz), 3.51(2H, t, J = 6.0 Hz), 3.60(2H, t, J = 4.4 Hz), 6.76(2H, d, J = 9.2 Hz), 7.21-7.28(2H, m), 7.35(1H, dd, J = 6.8Hz, 2.4 Hz), 7.84(2H, d, J = 9.2Hz), 9.53(1H, br)
10	 (free)	NMR(DMSO-d_6): 1.85-1.94(2H, m), 2.26(3H, s), 2.43(2H, t, J=5.6Hz), 2.61(2H, t, J=4.8Hz), 3.51(2H, t, J=6.0Hz), 3.58(2H, t, J=4.8Hz), 4.68(2H, s), 6.16(1H, dd, J=7.6Hz, 1.2Hz), 6.24(1H, dd, J=8.0Hz, 1.2Hz), 6.70-6.81(3H, m), 7.86(1H, d, J=8.8Hz), 8.93(1H, br), 8.94(1H, s)
11	 (free)	NMR(DMSO-d_6): δ:3.88(3H, s), 6.70(1H, dd, J = 7.7 Hz, 8.7 Hz), 7.14(2H, d, J = 8.9 Hz), 7.17 - 7.21(2H, m), 7.43(1H, dd, J = 1.4 Hz, 7.7 Hz), 7.97(1H, dd, J = 1.4 Hz, 8.7 Hz), 8.13(2H, d, J = 8.9 Hz)
12	 (free)	NMR(DMSO-d_6): δ:3.83 - 3.86(2H, m), 3.84(3H, s), 6.68 - 6.72 (1H,m), 6.72 - 6.78(1H, m), 7.06(2H, d, J = 8.7 Hz), 7.06 - 7.12(2H, m), 8.05(2H, d, J = 8.7 Hz), 9.63 - 9.67(1H, br)
13	 (free)	NMR(DMSO-d_6): δ:5.33(4H, s), 7.31 - 7.45 (10H,m), 7.61(1H, dd, J = 1.4 Hz, 7.5 Hz), 7.68(1H, t, J = 7.9 Hz), 7.74(1H, dd, J = 1.5 Hz, 8.2 Hz)
14	 (free)	NMR(DMSO-d_6): δ:5.32(2H, s), 7.31 - 7.44 (5H,m), 7.56(1H, dd, J = 1.7 Hz, 7.3 Hz), 7.64(1H, t, J = 7.9 Hz), 7.68(1H, dd, J = 1.7 Hz, 8.3 Hz)
15	 (free)	NMR($CDCl_3$): δ:5.23(2H, s), 7.22 - 7.26 (2H,m), 7.31 - 7.39 (5H,m), 7.46(1H, t, J = 8.3 Hz), 7.69(1H, dd, J = 2.7 Hz, 9.1 Hz), 8.03(1H, d, J = 2.9 Hz), 8.26(1H, d, J = 8.8 Hz), 9.01(1H, brs)
16	 (free)	NMR(DMSO-d_6): δ:5.93(2H, s), 6.44(1H, t, J = 7.9Hz), 6.82(1H, d, J = 7.7 Hz), 7.27(1H, d, J = 7.3 Hz), 7.93(1H, dd, J = 2.6 Hz, 9.0 Hz), 8.14(1H, d, J = 8.8 Hz), 8.41(1H, d, J = 2.4 Hz), 9.60(1H, s), 10.46(1H, s)
17	 (free)	NMR(DMSO-d_6): δ:6.04(2H, brs), 6.80(1H, d, J = 2.4 Hz), 7.36(1H, d, J = 2.0 Hz), 7.93(1H, dd, J = 2.5 Hz, 8.8 Hz), 8.11(1H, d, J = 9.3 Hz), 8.42(1H, d, J = 2.5 Hz), 10.16(1H, brs), 10.67(1H, s)

表２（続き）

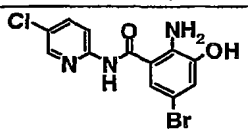
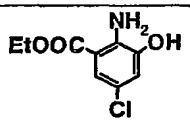
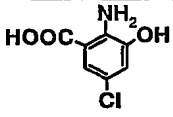
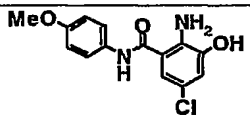
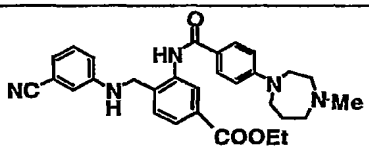
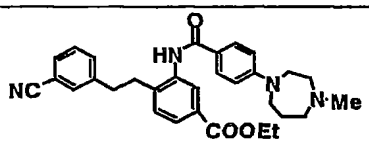
18	 (free)	NMR(DMSO-d_6): δ:6.06(2H, brs), 6.90(1H, d, J = 2.2 Hz), 7.47(1H, d, J = 2.2 Hz), 7.93(1H, dd, J = 2.8 Hz, 9.0 Hz), 8.10(1H, d, J = 9.0 Hz), 8.42(1H, d, J = 2.2 Hz), 10.15(1H, brs), 10.69(1H, s)
19	 (free)	NMR($CDCl_3$): δ:1.38(3H, t, J = 7.3 Hz), 4.33(2H, q, J = 7.3 Hz), 5.00 - 6.30(3H br), 6.81(1H, d, J = 2.0 Hz), 7.48(1H, d, J = 2.4 Hz)
20	 (free)	NMR(DMSO-d_6): δ:3.37(1.5H, brs), 6.78(1H, d, J = 2.4 Hz), 7.17(1H, d, J = 2.5 Hz), 8.34(1.5H, brs), 10.19(1H, s)
21	 (free)	NMR(DMSO-d_6): δ:3.74(3H, s), 5.93(2H, brs), 6.78(1H, d, J = 1.9 Hz), 6.91(2H, d, J = 9.3 Hz), 7.23(1H, d, J = 2.5 Hz), 7.59(2H, d, J = 9.3 Hz), 9.90(1H, s), 10.09(1H, brs)
22	 (free)	NMR($CDCl_3$): δ:1.39(3H, t, J = 7.4 Hz), 1.97 - 2.06(2H, m), 2.38(3H, s), 2.53 - 2.59(2H, m), 2.68 - 2.73(2H, m), 3.51(2H, t, J = 6.4 Hz), 3.57 - 3.63(2H, m), 4.34 - 4.42(5H, m), 6.58(2H, d, J = 8.8 Hz), 6.96 - 7.01(2H, m), 7.12(1H, d, J = 7.8 Hz), 7.31(1H, t, J = 7.8 Hz), 7.40(1H, d, J = 8.3 Hz), 7.65 (2H, d, J = 8.7 Hz), 7.81(1H, dd, J = 1.5 Hz, 7.8 Hz), 8.67(1H, d, J = 2.0 Hz), 8.85(1H, s), FAB-MS(m/z): 512$(M+H)^+$
23	 (free)	NMR($CDCl_3$): δ: 1.37(3H, t, J=7.1Hz), 2.43-2.54(2H, br), 2.76(3H, s), 2.93-3.01(4H, m), 3.14-3.22(2H, br), 3.23-3.29(2H, br), 3.59(2H, t, J=6.4Hz), 3.89-3.95(2H, m), 4.33(2H, q, J=7.1Hz), 6.72(2H, d, J=8.9Hz), 7.20(1H, d, J=7.3Hz), 7.27-7.35(3H, m), 7.41(1H, d, J=7.3Hz), 7.68-7.73(1H, m), 7.75(2H, d, J=8.3Hz), 7.85(1H, dd, J=1.8Hz, 8.3Hz), 8.23(1H, s) FAB-MS(m/z): 511 $(M+H)^+$

表3

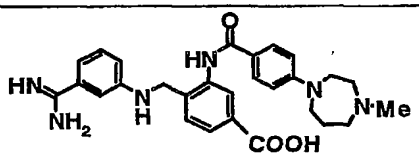
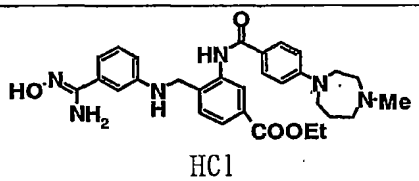
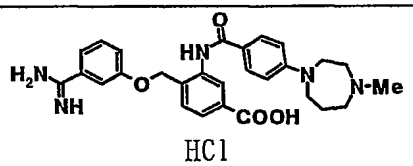
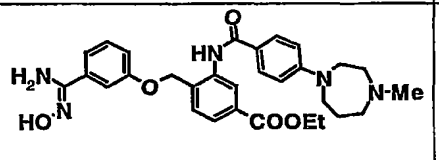
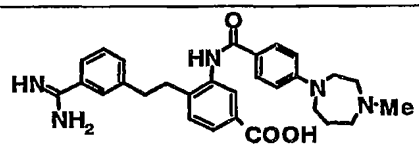
Ex	structure(salt)	DATA
1	 HCl	NMR(DMSO-d_6): δ:2.16-2.26(2H, br), 2.67(3H, s), 2.95 - 3.49(5H, br), 3.54(2H, t, J = 6.3 Hz), 3.73-3.86(2H, br), 4.44(2H, d, J = 5.3 Hz), 6.79 - 6.87(4H, m), 6.94(1H, d, J = 7.3 Hz), 6.98 (1H, s), 7.26(1H, t, J = 8.3 Hz), 7.44(1H, d, J = 7.8 Hz), 7.75(1H, dd, J = 2.0 Hz, 7.8 Hz), 7.94 (2H, d, J = 9.2 Hz), 7.98(1H, d, J = 1.9 Hz), 9.07(2H, s), 9.22(2H, s), 9.98(2H, s) FAB-MS(m/z): 501 $(M+H)^+$
2	 HCl	NMR(DMSO-d_6): δ:1.31(3H, t, J = 7.3 Hz), 2.79(3H, d, J = 4.4 Hz), 4.31(2H, q, J = 7.3 Hz), 4.43(2H, s), 6.76 - 6.91(6H, m), 7.25(1H, t, J = 8.4 Hz), 7.46(1H, d, J = 8.3 Hz), 7.77(1H, dd, J = 8.3, 1.4 Hz), 7.96(2H, d, J = 8.8 Hz), 8.01(1H, d, J = 1.4 Hz), FAB-MS(m/z): 545 $(M+H)^+$
3	 HCl	NMR(DMSO-d_6): δ: 2.02 - 2.09(2H, m), 2.76 - 2.84(2H, m), 2.87 - 2.98(2H, m), 3.32(3H, br s), 3.51 - 3.55(2H, m), 3.68 - 3.73(2H, m), 5.31(2H, s), 6.81(2H, d, J = 8.8 Hz), 7.31(1H, dd, J = 2.4 Hz , 8.4 Hz), 7.40(1H, d, J = 8.0 Hz), 7.46 - 7.49(1H, m), 7.50 - 7.54(1H, m), 7.62(1H, d, J = 8.4 Hz), 7.82(1H, dd, J = 2.0 Hz , 8.0 Hz), 7.89 (2H, d, J = 8.8 Hz), 8.03 (1H, d, J = 1.6 Hz), 9.33(4H, br s), 9.90(1H, s) FAB-MS(m/z): 502 $(M+H)^+$
4	 HCl	NMR(DMSO-d_6): δ: 1.33(3H, t, J = 7.4 Hz), 2.79(3H, s), 4.32(2H, q, J = 7.3 Hz), 5.26(2H, s), 6.86(2H, d, J = 8.8 Hz), 7.03 - 7.08(1H, m), 7.26 - 7.37(3H, m), 7.67(1H, d, J = 8.4 Hz), 7.84(1H, dd, J = 1.6 Hz , 8.4 Hz), 7.91 (2H, d, J = 8.8 Hz), 8.10 (1H, d, J = 1.6 Hz), FAB-MS(m/z): 546 $(M+H)^+$
5	 HCl	NMR(DMSO-d_6): δ: 2.12-2.24(1H, m), 2.38-2.49(1H, m), 2.79(3H, d, J=4.9Hz), 3.92-3.99(2H, m), 3.01-3.20(4H, m), 3.39-3.58(4H, m), 3.76-3.85(1H, m), 3.90-4.03(1H, m), 6.86(2H, d, J=9.3Hz), 7.41(1H, d, J=8.3Hz), 7.43-7.49(2H, m), 7.61-7.67(1H, m), 7.75(2H, dd, J=1.5Hz, 9.3Hz), 7.88(1H, d, J=1.5Hz), 7.98(2H, d, J=9.3Hz), 9.35(2H, s), 9.45(2H, s), 9.91(1H, s), 11.37(1H, s) FAB-MS(m/z): 500 $(M+H)^+$

表３（続き）

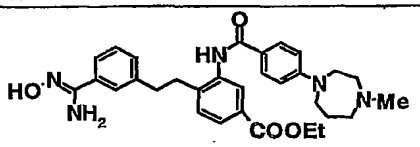
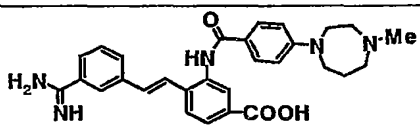
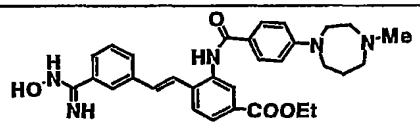
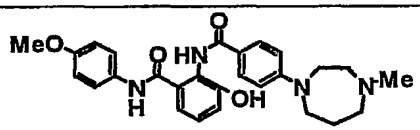
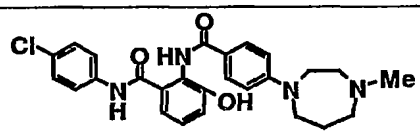
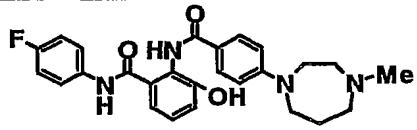
6	 HCl	NMR(DMSO-d_6): δ: 1.32(3H, t, J=7.0Hz), 2.78(3H, s), 4.31(2H, q, J=7.0Hz), 6.86(2H, d, J=8.8Hz), 7.40-7.46(3H, m), 7.53(1H, dt, J=1.9Hz, 7.1Hz), 7.62(1H, s), 7.76(1H, dd, J=1.9Hz, 7.1Hz), 7.90(1H, d, J=1.4Hz), 7.96(2H, d, J=8.8Hz) FAB-MS(m/z): 544 $(M+H)^+$
7	 HCl	NMR(DMSO-d_6): δ: 2.79(3H, d, J = 4.8 Hz), 6.87(2H, d, J = 8.8 Hz), 7.43(1H, d, J = 16.0 Hz), 7.53(1H, d, J = 16.0 Hz), 7.60 - 7.64(1H, m), 7.73(1H, d, J = 8.0 Hz), 7.83(1H, dd, J = 1.6 Hz , 8.4 Hz), 7.89(1H, d, J = 7.6 Hz), FAB-MS(m/z): 498 $(M+H)^+$
8	 HCl	NMR(DMSO-d_6): δ: 1.33(3H, t, J = 7.2 Hz), 2.80(3H, d, J = 4.8 Hz), 4.34(2H, q, J = 7.2 Hz), 6.88(2H, d, J = 9.2 Hz), 7.42 - 7.51(2H, m), 7.58 - 7.65(2H, m), 7.84 - 7.87(2H, m), 7.90(1H, s), 7.96 - 8.01(4H, m) FAB-MS(m/z): 542 $(M+H)^+$
9	 HCl	NMR(DMSO-d_6): δ:2.10 - 2.41(2H, m), 2.78(3H, s), 3.02 - 3.22(2H, m), 3.35 - 3.57(4H, m), 3.67 - 3.81(4H, m), 3.87 - 3.99(1H, m), 6.80 - 6.95(4H, m), 7.11(1H, d, J = 7.3 Hz), 7.17 - 7.28(2H, m), 7.57(2H, d, J = 8.8 Hz), 7.85 (2H, d, J = 8.8 Hz), 10.02(1H, s), 10.19(1H, s), 10.41(1H, s), 10.64(1H, brs) FAB-MS(m/z): 475 $(M+H)^+$
10	 HCl	NMR(DMSO-d_6): δ: 2.78(3H, s), 6.84(2H, d, J = 9.3 Hz), 7.10 - 7.13(1H, m), 7.15 - 7.18(1H, m), 7.22 - 7.26(1H, m), 7.36(2H, d, J = 8.8 Hz), 7.71 (2H, d, J = 8.7 Hz), 7.85 (2H, d, J = 8.8 Hz) FAB-MS(m/z): 479 $(M+H)^+$
11	 HCl	NMR(DMSO-d_6): δ:2.10 - 2.22(1H, m), 2.28 - 2.41(1H, m), 2.77(3H, d, J = 4.9 Hz), 3.02 - 3.21(2H, m), 3.38 - 3.57(4H, m), 3.75(1H, dd, J = 9.7 Hz, 16.1 Hz), 3.93(1H, dd, J = 2.9 Hz, 16.6 Hz), 6.85(2H, d, J = 8.8 Hz), 7.09 - 7.27(5H, m), 7.69(2H, dd, J = 5.1 Hz, 9.1 Hz), 7.85 (2H, d, J = 8.8 Hz), 9.75 - 10.10(1H, br), 10.14(1H, s), 10.36(1H, s), 10.86(1H, brs) FAB-MS(m/z): 463 $(M+H)^+$

表３（続き）

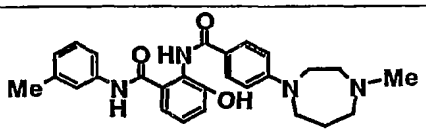
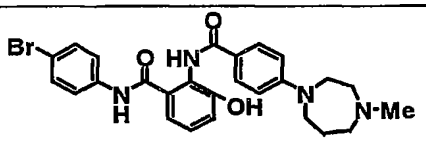
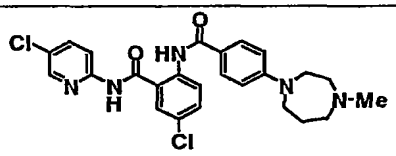
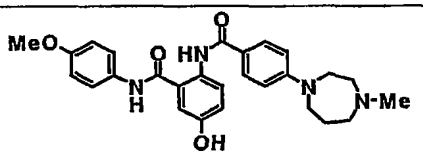
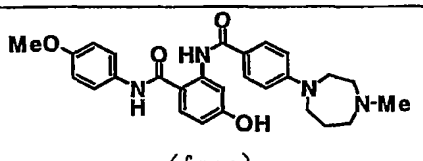
12	 HCl	NMR(DMSO-d_6): δ:2.11 - 2.40(2H, m), 2.27(3H, s), 2.78(3H, s), 3.01 - 3.22(2H, m), 3.38 - 3.55(4H, m), 3.73(1H, dd, J = 9.7 Hz, 16.1 Hz), 3.93(1H, d, J = 15.1 Hz), 6.83 - 6.91(3H, m), 7.11(1H, dd, J = 1.4 Hz, 8.3 Hz), 7.15 - 7.20(2H, m), 7.24 (1H, t, J = 7.8 Hz), 7.44(1H, d, J = 8.3 Hz), 7.49(1H, s), 7.86(2H, d, J = 8.8 Hz), 9.96(1H, s), 10.14(1H, s), 10.17(1H, s), 10.54(1H, brs) FAB-MS(m/z): 459$(M+H)^+$
13	 HCl	NMR(DMSO-d_6): δ:2.79(3H, d, J = 2.4 Hz), 6.84(2H, d, J = 9.3 Hz), 7.11(1H, dd, J = 1.3 Hz, 8.1 Hz), 7.16(1H, d. J = 6.8 Hz), 7.24 (1H, t, J = 7.8 Hz), 7.48(2H, d, J = 8.8 Hz), 7.65(2H, d, J = 8.8 Hz), 7.84(2H, d, J = 8.8 Hz), 9.95(1H, s), 9.97(1H, s), 10.39(1H, s), 10.48 - 10.65(1H, br) FAB-MS(m/z): 523$(M+H)^+$
14	 HCl	NMR(DMSO-d_6): δ:2.12 - 2.20(1H, m), 2.32 - 2.43(1H, m), 2.78(3H, d, J = 4.8 Hz), 3.05 - 3.20(2H, m), 3.39 - 3.56(4H, m), 3.73 - 3.82(1H, m), 3.91 - 3.97(1H, m), 6.90(2H, d, J = 8.7 Hz), 7.65(1H, dd, J = 2.4 Hz , 8.8 Hz), 7.79(2H, d, J = 8.8 Hz), 7.99 - 8.02(2H, m), 8.11 (1H, d, J = 8.8 Hz), 8.43(1H, d, J = 8.8 Hz), 8.48(1H, d, J = 2.5 Hz), 10.94(1H, br s), 11.23(1H, s), 11.29(1H, s) FAB-MS(m/z): 498$(M)^+$
15	 (free)	NMR(DMSO-d_6): δ:2.25(3H, s), 3.75(3H, s), 6.79(2H, d, J = 8.8 Hz), 6.91 - 7.01(3H, m), 7.24(1H, d, J = 2.5 Hz), 7.61(2H, d. J = 8.8 Hz), 7.69 (2H, d, J = 8.8 Hz), 8.28(1H, d, J = 8.8 Hz), FAB-MS(m/z): 475$(M+H)^+$
16	 (free)	NMR(DMSO-d_6): δ:2.25 (3H, s), 3.76 (3H, s), 6.55 (1H, dd, J = 8.8, 2.4 Hz), 6.82 (2H, d, J = 9.3 Hz), 6.95 (2H, d, J = 8.8 Hz), 7.57 (2H, d, J = 8.8 Hz), 7.74 (2H, d, J = 9.3Hz), 7.84 (1H, d, J = 8.8 Hz), 8.27 (1H, d, J = 2.4 Hz), FAB-MS(m/z): 475 $(M+H)^+$

表３（続き）

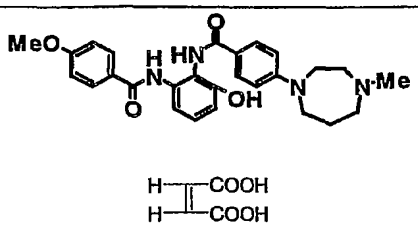
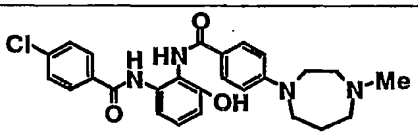
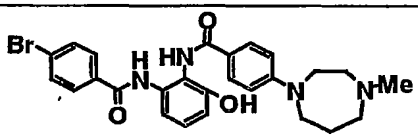
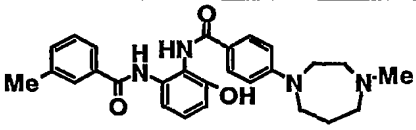
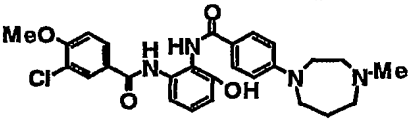
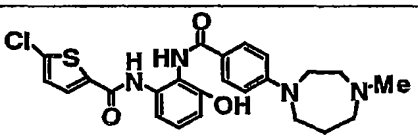
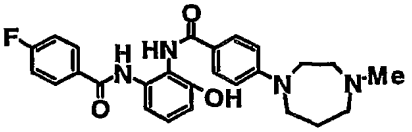
17		NMR(DMSO-d_6)： δ：2.11 - 2.20(2H, m), 2.83(3H, s), 3.20 - 3.45(4H, m), 3.52(2H, t, J = 6.0 Hz), 3.72 - 3.88(5H, m), 6.03(2H, s), 6.80(1H, d, J = 8.0 Hz), 6.85(2H, d, J = 8.8 Hz), 7.04(2H, d, J = 8.8 Hz), 7.14(1H, t, J = 8.0 Hz), 7.24(1H, d, J = 8.0 Hz), 7.85(2H, d, J = 8.8 Hz), 7.91(2H, d, J = 8.8 Hz), 9.47(1H, s), 9.67(1H, s), 9.77(1H, s) FAB-MS(m/z)：475 $(M+H)^+$
18	 HCl	NMR(DMSO-d_6)： δ：2.79(3H, s), 6.82 - 6.86(3H, m), 7.13 - 7.17(1H, m), 7.22(1H, d, J = 8.3 Hz), 7.58(2H, d, J = 8.3 Hz), 7.89 - 7.93(4H, m), FAB-MS(m/z)：479 $(M+H)^+$
19	 HCl	NMR(DMSO-d_6)： δ：2.79(3H, s), 6.82 - 6.86(3H, m), 7.13 - 7.17(1H, m), 7.22(1H, d, J = 7.8 Hz), 7.72(2H, d, J = 8.3 Hz), 7.83(2H, d, J = 8.3 Hz), 7.92(2H, d, J = 8.8 Hz) FAB-MS(m/z)：523 , 525 $(M+H)^+$
20	 HCl	NMR(DMSO-d_6)： δ：2.79(3H, s), 6.82(1H, d, J = 8.3 Hz), 6.86(2H, d, J = 8.8 Hz), 7.13 - 7.17(1H, m), 7.27(1H, d, J = 8.4 Hz), 7.36 - 7.79(2H, m), 7.64 - 7.68(2H, m), 7.95(2H, d, J = 8.3 Hz), 9.56(1H, s) FAB-MS(m/z)：459 $(M+H)^+$
21	 HCl	NMR(DMSO-d_6)： δ：2.69(3H, s), 3.92(3H, s), 6.81 - 6.84(3H, m), 7.14(1H, dd, J = 7.8, 8.3Hz), 7.22(1H, d, J = 7.8Hz), 7.27(1H, d, J = 8.8Hz), 7.88(1H, dd, J = 2.0, 8.3Hz), 7.93(2H, d, J = 8.8)), 7.95(1H, d, J = 2.0Hz) FAB-MS m/z：509 (M^+)
22	 HCl	NMR(DMSO-d_6)： δ：2.80(3H, d, J =3.9 Hz), 6.79 - 6.88(3H, m), 7.10 - 7.18(2H, m), 7.24(1H, d, J = 3.9Hz), 7.72(1H, d, J = 3.9Hz), 7.95(2H, d, J = 8.8Hz), FAB-MS m/z：485 (M^+)
23	 HCl	NMR(DMSO-d_6)： δ：2.78(3H, s), 6.82 - 6.85(3H, m), 7.13 - 7.17(1H, m), 7.22(1H, d, J = 7.8 Hz), 7.32 - 7.37(2H, m), 7.93(2H, d, J = 8.8 Hz), 7.95 - 7.99(2H, m) FAB-MS(m/z)：463(M+H)$^+$

表３（続き）

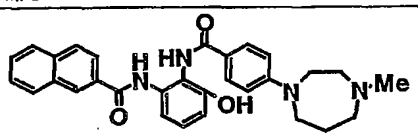
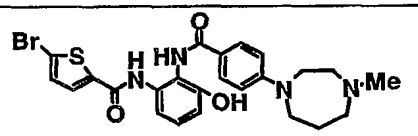
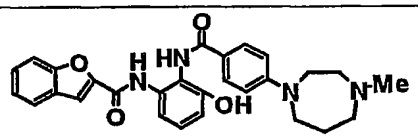
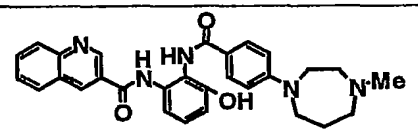
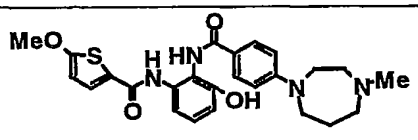
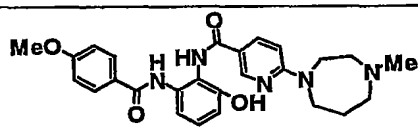
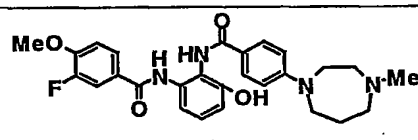
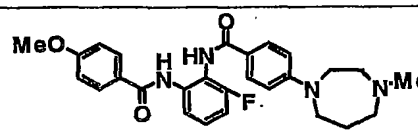
24	 HCl	NMR(DMSO-d_6)： δ：2.76(3H, s), 6.83 - 6.87(3H, m), 7.16 - 7.20(1H, m), 7.31(1H, d, J = 8.3 Hz), 7.59 - 7.66(2H, m), 7.94 - 8.04(6H, m), 8.50(1H, s), FAB-MS(m/z)：495 $(M+H)^+$
25	 HCl	NMR(DMSO-d_6)： δ：2.80(3H, d, J =4.3 Hz), 6.81 - 6.86(3H, m), 7.11 - 7.17(2H, m), 7.33(1H, d, J = 3.9Hz), 7.66(1H, d, J = 4.4Hz), 7.94(2H, d, J = 8.8Hz) FAB-MS (m/z)：529, 531 $(M+H)^+$
26	 HCl	NMR(DMSO-d_6)： δ：2.75(3H, s), 6.84 - 6.88(3H, m), 7.15 - 7.19(1H, m), 7.33 - 7.37(2H, m), 7.47 - 7.51(1H, m), 7.57(1H, d, J = 8.3 Hz), 7.67(1H, s), 7.80(1H, d, J = 7.8 Hz), 8.00(2H, d, J = 8.3 Hz) FAB-MS(m/z)：485 $(M+H)^+$
27	 HCl	NMR(DMSO-d_6)： δ：2.75(3H, d, J = 4.9 Hz), 6.83(2H, d, J = 9.3 Hz), 6.88(1H, d, J = 7.8Hz), 7.17 - 7.21(1H, m), 7.29(1H, d, J = 7.8 Hz), 7.79 - 7.82(1H, m), 7.98 - 8.01(3H, m), 8.17 - 8.20(2H, m), 9.16(1H, s), 9.44(1H, d, J = 1.9 Hz) FAB-MS (m/z)：496 $(M+H)^+$
28	 HCl	NMR(DMSO-d_6)： δ：2.80(3H, d, J = 2.4 Hz), 6.40(1H, d, J = 3.9 Hz), 6.80(1H, dd, J = 1.5Hz, 7.8Hz), 6.86(2H, d, J = 8.8 Hz), 7.10 - 7.18(2H, m), 7.53(1H, d, J = 3.9 Hz), 7.94(2H, d, J = 8.8Hz) FAB-MS (m/z)：481 $(M+H)^+$
29	 HCl	NMR(DMSO-d_6)： δ：2.79(3H, d, J = 5.9 Hz), 3.81(3H, s), 6.80(1H, d, J = 8.3 Hz), 6.85(1H, d, J = 8.8 Hz), 7.03(2H, d, J = 8.8 Hz), 7.12 - 7.17(1H, m), 7.24- 7.27(1H, m), 7.86(2H, d, J = 8.8 Hz), 8.18(1H, d, J = 8.7 Hz), 8.79(1H, s) FAB-MS(m/z)：476 $(M+H)^+$
30	 HCl	NMR(DMSO-d_6)： δ：2.79(3H, s), 6.82 - 6.86(3H, m), 7.12 - 7.16(1H, m), 7.22(1H, d, J = 7.8 Hz), 7.27 - 7.31(1H, m), 7.72 - 7.77(2H, m), 7.94(2H, d, J = 8.3 Hz), FAB-MS(m/z)：493 $(M+H)^+$
31	 HCl	NMR(DMSO-d_6)： δ：2.79(3H, d, J = 5.9 Hz), 3.05 - 3.21(2H, m), 3.82(3H, s), 6.85(2H, d, J = 9.3 Hz), 7.03(2H, d, J = 8.8 Hz), 7.13 - 7.18(1H, m), 7.31 - 7.37(1H, m), 7.55 - 7.59(1H, m), 7.89(2H, d, J = 8.8 Hz), 7.94(2H, d, J = 8.7 Hz) FAB-MS(m/z)：477 $(M+H)^+$

表３（続き）

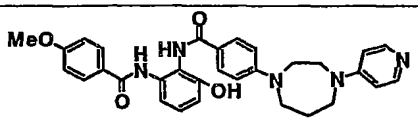
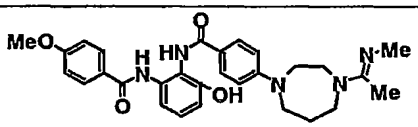
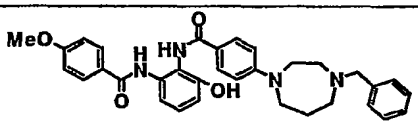
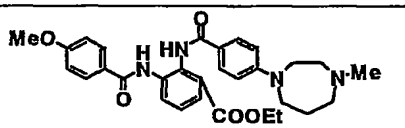
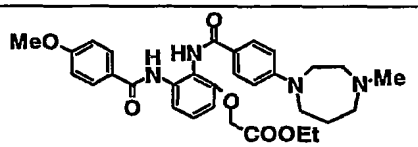
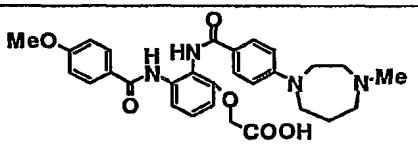
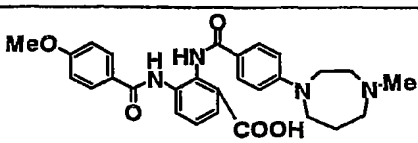
32	 HCl	NMR(DMSO-d_6): δ:1.82 - 2.01(2H, m), 3.46 - 3.89(11H, m), 6.80(1H, d, J = 7.8 Hz), 6.86(2H, d, J = 8.8 Hz), 6.97 - 7.21(5H, m), 7.25(1H, d, J = 8.3 Hz), 7.78 - 7.94(4H, m), 8.18(2H, s), 9.51(1H, s), 9.66(1H, brs), 9.82(1H, s), 13.46(1H, brs), FAB-MS(m/z): 538$(M+H)^+$
33	 HCl	NMR(DMSO-d_6): δ:2.24(1.5H, s), 2.26(1.5H, s), 2.84 - 2.95(3H, m), 6.81(1H, d, J = 7.8 Hz), 6.84 - 6.93(2H, m), 7.04(2H, d, J = 8.8 Hz), 7.14(1H, t, J = 8.3 Hz), 7.24(1H, d, J = 8.3 Hz), 7.87(2H, d, J = 8.8 Hz), 7.91(2H, d, J = 8.9 Hz) FAB-MS(m/z): 516$(M+H)^+$
34	 HCl	NMR(DMSO-d_6): δ:6.80 (1H, dd, J = 0.9 Hz, 8.3 Hz), 6.85(2H, d, J = 8.7 Hz), 7.03(2H, d, J = 8.7 Hz), 7.14(1H, t, J = 8.3 Hz), 7.24(1H, d, J = 7.8 Hz), 7.43 - 7.51(3H, m), 7.54 - 7.61(2H, m), 7.86(2H, d, J = 8.7 Hz), 7.91(2H, d, J = 8.7 Hz) FAB-MS(m/z): 551$(M+H)^+$
35	 HCl	NMR(DMSO-d_6): δ: 1.14(3H, t, J = 6.8 Hz), 2.80(3H, d, J = 4.4 Hz), 3.83(3H, s), 4.16(2H, q, J = 7.2 Hz), 6.86(2H, d, J = 8.8 Hz), 7.06(2H, d, J = 8.8 Hz), 7.39 - 7.43(1H, m), 7.68(1H, dd, J = 1.5 Hz , 7.8 Hz), 7.86 - 7.88(3H, m), 7.94(2H, d, J = 8.7 Hz) FAB-MS(m/z): 531$(M+H)^+$
36	 HCl	NMR(DMSO-d_6): δ: 1.21(3H, t, J =7.3 Hz), 2.78(3H, d, J = 4.9 Hz), 4.17(2H, q, J = 7.3 Hz), 4.83(2H, s), 6.86(2H, d, J = 9.3 Hz), 6.92(1H, d, J = 7.3 Hz), 7.04(2H, d, J = 8.8 Hz), 7.25 - 7.29(1H, m), 7.49(1H, d, J = 7.8 Hz), 7.86(2H, d, J = 8.8 Hz), 7.93(2H, d, J = 8.8 Hz) FAB-MS(m/z): 561$(M+H)^+$
37	 HCl	NMR(DMSO-d_6): δ: 2.78(3H, s), 4.75(2H, s), 6.86(2H, d, J = 9.3 Hz), 6.94(1H, d, J = 7.3 Hz), 7.04(2H, d, J = 8.8 Hz), 7.25 - 7.30(1H, m), 7.50(1H, d, J = 7.9 Hz), 7.85(2H, d, J = 8.8 Hz), 7.95(2H, d, J = 8.8 Hz) FAB-MS(m/z): 533$(M+H)^+$
38	 HCl	NMR(DMSO-d_6): δ: 2.77(3H, d, J = 4.4 Hz), 6.87(2H, d, J = 8.7 Hz), 7.05(2H, d, J = 8.8 Hz), 7.38 - 7.42(1H, m), 7.75(1H, d, J = 7.3 Hz), 7.88 - 7.94(5H, m) FAB-MS(m/z): 503$(M+H)^+$

表３（続き）

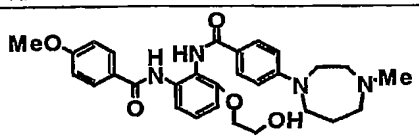
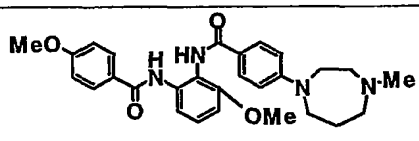
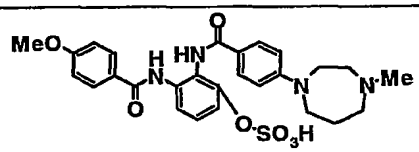
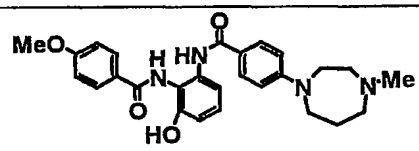
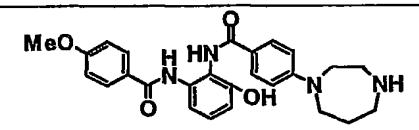
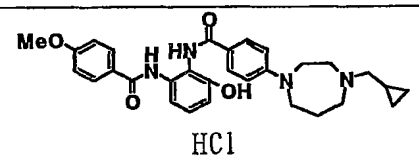
39	 HCl	NMR(DMSO-d_6): δ: 2.12 - 2.22(1H, m), 2.26 - 2.39(1H, m), 2.79(3H, d, J = 3.9 Hz), 3.05 - 3.21(2H, m), 3.39 - 3.55(4H, m), 3.66 - 3.79(3H, m), 3.81(3H, s), 3.90 - 3.97(1H, m), 4.11(2H, t, J = 4.9 Hz), 4.86(1H, br s), 6.86(2H, d, J = 8.8 Hz), 6.97(1H, d, J = 7.4 Hz), 7.04(2H, d, J = 8.8 Hz), 7.25 - 7.29(1H, m), 7.42(1H, d, J = 8.3 Hz), 7.86(2H, d, J = 8.7 Hz), 7.92(2H, d, J = 8.8 Hz), 9.55(1H, s), 9.89(1H, s), 10.67(1H, br s) FAB-MS(m/z): 519$(M+H)^+$
40	 HCl	NMR(DMSO-d_6): δ: 2.79(3H, d, J = 4.9 Hz), 6.85(2H, d, J = 8.8 Hz), 6.95(1H, d, J = 8.3 Hz), 7.02(2H, d, J = 8.7 Hz), 7.29(1H, t, J = 8.3 Hz), 7.42(1H, d, J = 8.3 Hz), 7.84(2H, d, J = 8.8 Hz), 7.92(2H, d, J = 8.8 Hz) FAB-MS(m/z): 489 $(M+H)^+$
41	 (free)	NMR(DMSO-d_6): δ:2.08 - 2.23(2H, m), 2.84(3H, s), 3.10 - 4.05(11H, m), 6.93(2H, d, J = 9.3 Hz), 6.95(1H, d, 8.3 Hz), 7.01-7.08(3H, m), 7.28(1H, t, J = 8.3 Hz), 7.7(1H, dd, J = 1.4 Hz, 8.3 Hz), 7.83(2H, d, J = 8.8 Hz), 7.92(2H, d, J = 9.2Hz), 9.4(1H, brs), 9.91(1H, s), 10.37(1H, s) FAB-MS(m/z): 553 $(M-H)^+$
42	 HCl	NMR(DMSO-d_6): δ:2.79(3H, d = 4.9 Hz), 6.78(1H, d, J = 7.8 Hz), 6.82(2H, d, J = 8.8 Hz), 7.06(2H, d, J = 8.8 Hz), 7.13(1H, t, J = 7.8 Hz), 7.30(1H, d, J = 7.8 Hz), 7.75(2H, d, J = 8.8 Hz), 8.01(2H, d, J = 8.8 Hz), FAB-MS(m/z): 475$(M+H)^+$
43	 HCl	NMR(DMSO-d_6): δ: 6.81(1H, dd, J = 1.5, 8.3 Hz), 6.86(2H, d, J = 8.8 Hz), 7.03(2H, d, J = 8.7 Hz), 7.13(1H, t, J = 8.3 Hz), 7.25(1H, d, J = 8.3 Hz), 7.87(2H, d, J = 8.8 Hz), 7.93(2H, d, J = 8.8 Hz), FAB-MS(m/z): 461$(M+H)^+$
44	 HCl	NMR(DMSO-d_6): δ: 0.35 - 0.43(2H, m), 0.61 - 0.67(2H, m), 1.08 - 1.15(1H, m)6.81(1H, dd, J = 1.0 Hz , 8.8 Hz), 6.86(2H, d, J = 8.8 Hz), 7.03(2H, d, J = 8.3 Hz), 7.11 - 7.16(1H, m), 7.24(1H, dd, J = 1.0 Hz , 7.9 Hz), 7.87(2H, d, J = 8.8 Hz), 7.93(2H, d, J = 8.8 Hz), FAB-MS(m/z): 515$(M+H)^+$

表３（続き）

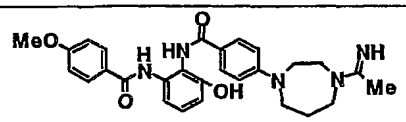
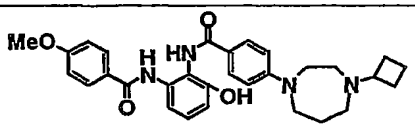
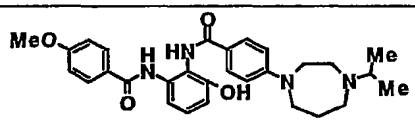
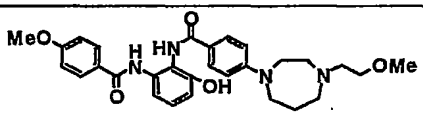
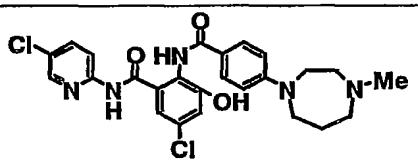
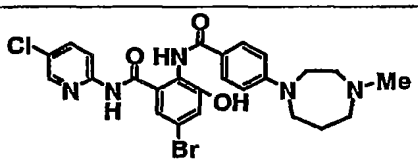
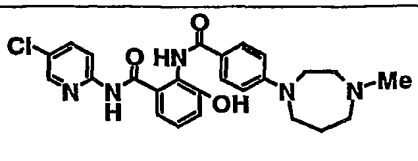
45	 HCl	NMR(DMSO-d_6)： δ:6.81(1H, d, J = 8.3 Hz), 6.84 - 6.93(2H, m), 7.03(2H, d, J = 9.3 Hz), 7.13(1H, t, J = 8.3 Hz), 7.25(1H, d, J = 8.3 Hz), 7.88(2H, d, J = 8.2 Hz), 7.92(2H, d, J = 8.3 Hz) FAB-MS(m/z)： 502$(M+H)^+$
46	 HCl	NMR(DMSO-d_6)： δ： 6.80 - 6.86(3H, m), 7.03(2H, d, J = 8.8 Hz), 7.11 - 7.16(1H, m), 7.24(1H, dd, J = 1.0 Hz , 7.8 Hz), 7.87(2H, d, J = 8.8 Hz), 7.93(2H, d, J = 8.8 Hz) FAB-MS(m/z)： 515$(M+H)^+$
47	 HCl	NMR(DMSO-d_6)： δ:1.21 - 1.28(6H, m), 6.80(1H, d, J = 7.9 Hz), 6.85(2H, d, J = 8.8 Hz), 7.03(2H, d, J = 8.8 Hz), 7.14(1H, t, J = 7.9 Hz), 7.24(1H, d, J = 7.8 Hz), 7.86(2H, d, J = 8.3 Hz), 7.92(2H, d, J = 8.8 Hz) FAB-MS(m/z)： 503$(M+H)^+$
48	 HCl	NMR(DMSO-d_6)： δ:6.73 - 6.88(3H, m), 7.03(2H, d, J = 8.8 Hz), 7.14(1H, t, J = 8.3 Hz), 7.24(1H, dd, J = 1.4 Hz, 8.3 Hz), 7.87(2H, d, J = 8.8 Hz), 7.93(2H, d, J = 8.8 Hz), FAB-MS(m/z)： 519$(M+H)^+$
49	 HCl	NMR(DMSO-d_6)： δ:2.10 - 2.21(1H, m), 2.23 - 2.37(1H, m), 2.79(3H, d, J = 4.9 Hz), 3.02 - 3.21(2H, m), 3.37 - 3.56(4H, m), 3.66 - 3.95(2H, m), 6.81(2H, d, J = 8.8 Hz), 7.15(2H, s), 7.82(2H, d, J = 8.8 Hz), 7.89(1H, dd, J = 2.5, 8.8 Hz), 8.08(1H, d, J = 8.8 Hz), 8.36(1H, d, J = 2.4 Hz), 9.51(1H, s), 10.33 - 10.63(2H, br), 10.68(1H, s) FAB-MS(m/z)： 514$(M+H)^+$
50	 HCl	NMR(DMSO-d_6)： δ:2.10 - 2.33(2H, m), 2.79(3H, s), 3.01 - 3.22(2H, m), 3.35 - 3.51(4H, m), 3.65 - 3.79(1H, m), 3.85 - 3.98(1H, m), 6.81(2H, d, J = 8.8 Hz), 7.27(2H, s), 7.82(2H, d, J = 9.3 Hz), 7.89(1H, dd, J = 2.5, 8.8 Hz), 8.08(1H, d, J = 9.2 Hz), 8.36(1H, d, J = 2.9 Hz), 9.50(1H, s), 10.37(1H, brs), 10.44(1H, s), 10.69(1H, s) FAB-MS(m/z)： 558, 560$(M+H)^+$
51	 HCl	NMR(DMSO-d_6)： δ： 2.22(2H, brs), 2.74(3H, s), 3.00 - 3.60(6H, m), 3.81(2H, brs), 6.82(2H, d, J = 9.3 Hz), 7.10 - 7.25(3H, m), 7.83(2H, d, J = 8.8 Hz), 7.90(1H, dd, J = 2.8 Hz, 9.1 Hz), 8.13(1H, d, J = 8.7 Hz), 8.35(1H, d, J = 2.5 Hz), 9.71(1H, s), 9.95(1H, s), 10.58(1H, s), 10.62 - 10.88(1H, br) FAB-MS(m/z)： 480$(M+H)^+$

表３（続き）

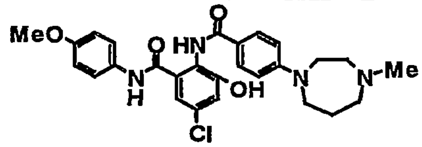
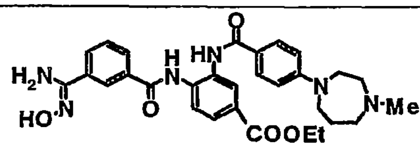
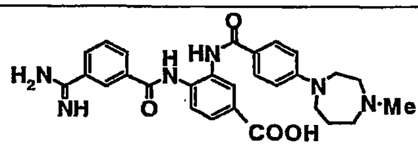
52	 HCl	NMR(DMSO-d_6): δ:2.10 - 2.34(2H, m), 2.81(3H, s), 3.01 - 3.25(2H, m), 3.35 - 3.60(4H, m), 3.62 - 3.79(4H, m), 3.82 - 4.00(1H, m), 6.84(2H, d, J = 9.3 Hz), 6.88(2H, d, J = 8.8 Hz), 7.12(1H, d, J = 2.5 Hz), 7.18(1H, d, J = 2.4 Hz), 7.54(2H, d, J = 9.3 Hz), 7.84(2H, d, J = 8.8 Hz), 9.86(1H, brs), 9.96(1H, s), 10.16(1H, s), 10.43(1H, s) FAB-MS(m/z): 509 $(M+H)^+$
53	 HCl	NMR(DMSO-d_6): δ: 1.35(3H, t, J = 7.3 Hz), 2.79(3H, d, J = 4.9 Hz), 4.35(2H, q, J = 7.3 Hz), 6.85(2H, d, J = 9.3 Hz), 7.68 - 7.74(1H, m), 7.82 - 7.88(2H, m), 7.92 - 7.98(3H, m), 8.19 - 8.24(1H, m), 8.27(1H, s), 8.38 (1H, s) FAB-MS(m/z): 559 $(M+H)^+$
54	 HCl	NMR(DMSO-d_6): δ: 2.79(3H, d, J = 4.9 Hz), 6.85(2H, d, J = 9.3 Hz), 7.76 - 7.84(3H, m), 7.98(2H, d, J = 8.8 Hz), 8.03(1H, d, J = 7.8 Hz), 8.25(1H, s), 8.31(1H, d, J = 7.8 Hz), 8.53(1H, s), FAB-MS(m/z): 515 $(M+H)^+$

表４

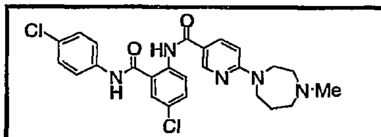
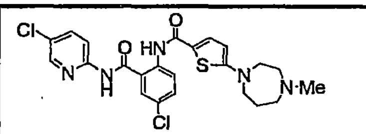
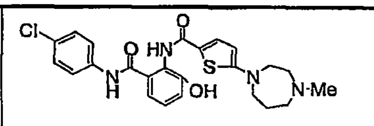
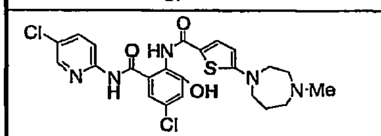
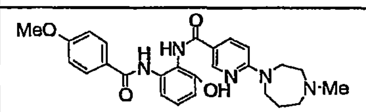
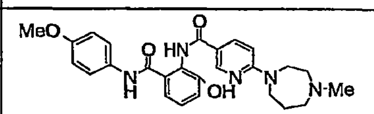
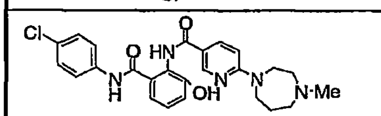
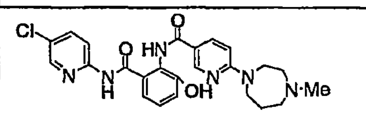
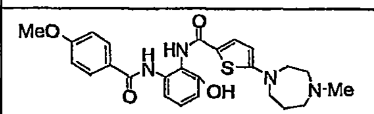
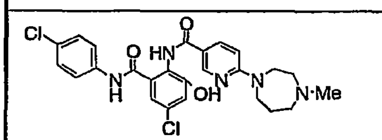
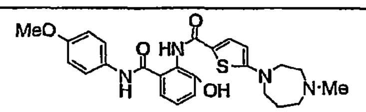
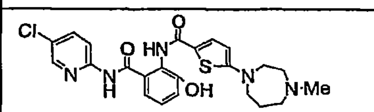
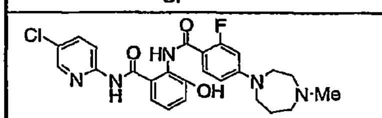
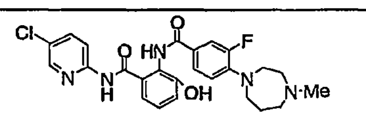
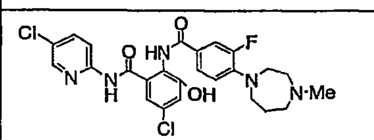
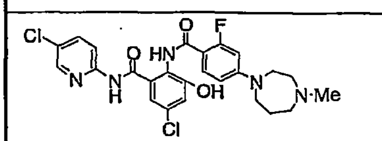
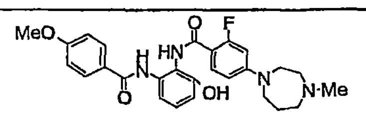
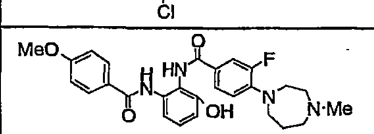
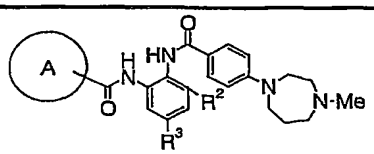
		
		
		
		
		
		

表5



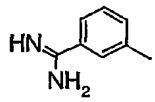
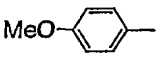
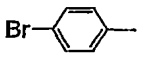
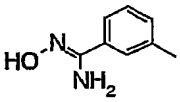
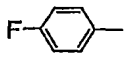
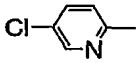
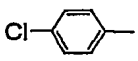
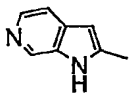
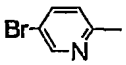
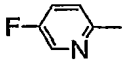
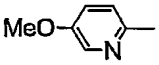
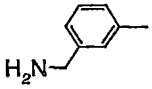
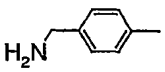
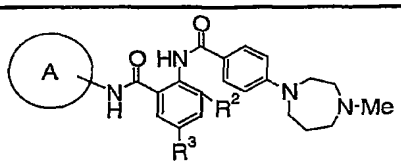
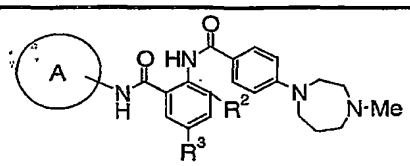
No.	A	R^2	R^3	No.	A	R^2	R^3
1		OH	Cl	32		OH	Cl
2		OH	H	33		H	Cl
3		H	Cl	34		OH	Br
4		OH	Br	35		H	Br
5		H	Br	36		OH	Cl
6		OH	F	37		H	Cl
7		H	F	38		OH	Br
8		OH	Cl	39		H	Br
9		OH	H	40		OH	Cl
10		H	Cl	41		H	Cl
11		OH	Br	42		OH	Br
12		H	Br	43		H	Br
13		OH	F	44		OH	Cl
14		H	F	45		H	Cl
15		OH	Cl	46		OH	Br
16		H	Cl	47		H	Br
17		OH	Br	48		OH	H
18		H	Br	49		OH	Cl
19		OH	Cl	50		H	Cl
20		H	Cl	51		OH	Br
21		OH	Br	52		H	Br
22		H	Br	53		OH	H
23		OH	H	54		OH	Cl
24		OH	Cl	55		H	Cl
25		H	Cl	56		OH	Br
26		OH	Br	57		H	Br
27		OH	H	58		OH	H
28		OH	Cl	59		OH	Cl
29		OH	H	60		OH	H
30		H	Cl	61		H	Cl
31		OH	Br	62		OH	Br

表５（続き）



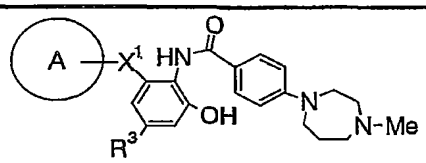
No.	A	R^2	R^3	No.	A	R^2	R^3
121		OH	Cl	151		H	Cl
122		OH	H	152		OH	Br
123		H	Cl	153		H	Br
124		OH	Br	154		OH	F
125		H	Br	155		OH	Cl
126		OH	F	156		H	Cl
127		H	F	157		OH	Br
128		OH	Cl	158		H	Br
129		OH	H	159		OH	Cl
130		H	Cl	160		H	Cl
131		OH	Br	161		OH	Br
132		H	Br	162		H	Br
133		OH	Cl	163		H	Br
134		H	Cl	164		OH	F
135		OH	Br	165		OH	Cl
136		H	Br	166		H	Cl
137		OH	Cl	167		OH	Br
138		H	Cl	168		H	Br
139		OH	Br	169		OH	H
140		H	Br	170		OH	Cl
141		OH	H	171		H	Cl
142		OH	Cl	172		OH	Br
143		H	Cl	173		H	Br
144		OH	Br	174		OH	H
145		H	Br	175		OH	F
146		OH	H	176		OH	Cl
147		OH	Cl	177		H	Cl
148		OH	H	178		OH	Br
149		OH	Br	179		H	Br
150		H	Cl	180		OH	H

表５（続き）



No.	A	R^2	R^3	No.	A	R^2	R^3
181		OH	Cl	211		OH	Cl
182		OH	H	212		OH	H
183		H	Cl	213		H	Cl
184		OH	Br	214		OH	Br
185		H	Br	215		H	Br
186		OH	Cl	216		OH	Cl
187		OH	H	217		OH	H
188		H	Cl	218		H	Cl
189		OH	Br	219		OH	Br
190		H	Br	220		H	Br
191		OH	Cl	221		OH	Cl
192		OH	H	222		OH	H
193		H	Cl	223		H	Cl
194		OH	Br	224		OH	Br
195		H	Br	225		H	Br
196		OH	Cl	226		OH	Cl
197		OH	H	227		OH	H
198		H	Cl	228		H	Cl
199		OH	Br	229		OH	Br
200		H	Br	230		H	Br
201		OH	Cl	231		OH	Cl
202		OH	H	232		H	Cl
203		H	Cl	233		OH	Br
204		OH	Br	234		H	Br
205		H	Br	235		OH	H
206		OH	Cl	236		OH	Cl
207		OH	H	237		H	Cl
208		H	Cl	238		OH	Br
209		OH	Br	239		H	Br
210		H	Br	240		OH	H

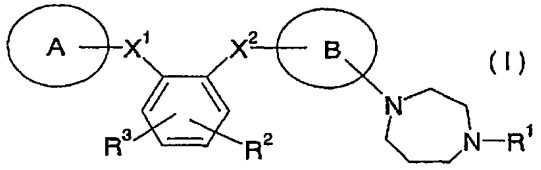
表6



No	A	X^1	R^3	No	A	X^1	R^3
1		$-CH_2-CH_2-$	H	32		$-CH_2-CH_2-$	H
2		$-CH_2-CH_2-$	Cl	33		$-CH_2-CH_2-$	Cl
3		$-NH-CH_2-$	H	34		$-NH-CH_2-$	H
4		$-NH-CH_2-$	Cl	35		$-NH-CH_2-$	Cl
5		$-O-CH_2-$	H	36		$-O-CH_2-$	H
6		$-O-CH_2-$	Cl	37		$-O-CH_2-$	Cl
7		(E) -CH=CH-	H	38		(E) -CH=CH-	H
8		(E) -CH=CH-	Cl	39		(E) -CH=CH-	Cl
9		$-CH_2-CH_2-$	H	40		$-CH_2-CH_2-$	H
10		$-CH_2-CH_2-$	Cl	41		$-CH_2-CH_2-$	Cl
11		$-NH-CH_2-$	H	42		$-NH-CH_2-$	H
12		$-NH-CH_2-$	Cl	43		$-NH-CH_2-$	Cl
13		$-O-CH_2-$	H	44		$-O-CH_2-$	H
14		$-O-CH_2-$	Cl	45		$-O-CH_2-$	Cl
15		(E) -CH=CH-	Cl	46		(E) -CH=CH-	Cl
16		$-CH_2-CH_2-$	H	47		$-CH_2-CH_2-$	H
17		$-CH_2-CH_2-$	Cl	48		$-CH_2-CH_2-$	Cl
18		$-NH-CH_2-$	H	49		$-NH-CH_2-$	H
19		$-NH-CH_2-$	Cl	50		$-NH-CH_2-$	Cl
20		$-O-CH_2-$	H	51		$-O-CH_2-$	H
21		$-O-CH_2-$	Cl	52		$-O-CH_2-$	Cl
22		(E) -CH=CH-	H	53		(E) -CH=CH-	H
23		(E) -CH=CH-	Cl	54		(E) -CH=CH-	Cl
24		$-CH_2-CH_2-$	H	55		$-CH_2-CH_2-$	H
25		$-CH_2-CH_2-$	Cl	56		$-CH_2-CH_2-$	Cl
26		$-NH-CH_2-$	H	57		$-NH-CH_2-$	H
27		$-NH-CH_2-$	Cl	58		$-NH-CH_2-$	Cl
28		$-O-CH_2-$	H	59		$-O-CH_2-$	H
29		$-O-CH_2-$	Cl	60		$-O-CH_2-$	Cl
30		(E) -CH=CH-	H	61		(E) -CH=CH-	H
31		(E) -CH=CH-	Cl	62		(E) -CH=CH-	Cl

Patent Claims.

1. Diazepane derivatives or salts thereof represented by following general formula (I).



(The symbols in above formula have the following meanings.
A ring and B ring: may be the same or different and denote aryl or heteroaryl each of which may have 1-3 substituents,
X1: -C(=O)=NR4-, -NR4-C(=O)-, -NR4-CH2-, -O-CH2-, -CH2-CH2, or -CH=CH-,
X2: -C(=O)=NR5-, or -NR5-C(=O)-,
R1: hydrogen atom, lower alkyl, -lower alkylene-O-lower alkyl, C3-8 cycloalkyl, aryl, heteroaryl, -lower alkylene-C3-8 cycloalkyl, -lower alkylene-aryl, -lower alkylene-heteroaryl, or -C(=NR6)-lower alkyl,
R2: -OH, -O-lower alkyl, -O-lower alkylene-OH, -O-SO2-OH, -O-lower alkylene-COOH, O-lower alkylene-COO-lower alkyl, -COOH, -COO-lower alkyl, or halogen atom,
R3: hydrogen atom, halogen atom, or lower alkyl,
R4, R5, and R6: may be the same or different and denote hydrogen atom, or lower alkyl)

2. Diazepane derivatives or salts thereof in accordance with Claim 1, wherein R2 is -OH.

3. Diazepane derivatives or salts thereof in accordance with Claim 1, wherein the A ring and B ring are the same or different, and comprise benzene ring, pyridine ring, naphthalene ring, thiophene ring, benzofuran ring or the quinoline ring each of which may have 1-3 substituents.

4. Diazepane derivatives or salts thereof in accordance with Claim 1, wherein the substituent of aryl or heteroaryl each of which may have 1-3 substituents comprises substituents selected from optionally substituted lower alkyl, lower alkenyl, lower alkynyl, C3-8 cycloalkyl, -O-optionally substituted lower alkyl, halogen atom, -NH2, -NH-lower alkyl, -N-(lower alkyl)2, -C(=NH)-NH2, -C(=N-OH)-NH2, -C(=NH)-NH-OH, -C(=NH)-NH-C(=O)-O-lower alkyl, -COOH, -C(=O)-O-optionally substituted lower alkyl, -C(=O)-O-optionally substituted C6-14 aryl, -C(=O)-O-optionally substituted heteroaryl, -CN, -NO2, -OH, -O-CO-optionally substituted lower alkyl, -O-CO-NH2, -O-CO-NH-lower alkyl, -O-CO-N-(lower alkyl)2, -SH, -C(=O)-NH2, -C(=O)-NH-(lower alkyl), -C(=O)-N-(lower alkyl)2.

5. Diazepane derivatives or salts thereof in accordance with Claim 1, which are selected from 3-hydroxy-4'-methoxy-2-{[4-(4-methyl-1,4-diazepan-1-yl) benzoyl] amino} benzanilide, 3-hydroxy-N1-(4-methoxybenzoyl)-N2-[4-(4-methyl-1,4-diazepan-1-yl) benzoyl]-1,2-phenylenediamine, 5-chloro-N-(5-chloro-2-pyridyl)-3-hydroxy-2-{[4-(4-methyl-1,4-diazepan-1-yl) benzoyl] amino} benzamide, 5-chloro-3-hydroxy-4'-methoxy-2-{[4-(4-methyl-1,4-diazepan-1-yl) benzoyl] amino} benzanilide, 5-bromo-N-(5-chloro-2-pyridyl)-3-hydroxy-2-{[4-(4-methyl-1,4-diazepan-1-yl) benzoyl] amino} benzamide.

6. Medicinal composition containing diazepane derivatives or salts thereof described in Claim 1 as effective ingredient.

7. Activated blood coagulating factor X inhibitor containing diazepane derivatives or salts thereof described in Claim 1 as effective ingredient.

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WO0174791

Publication Title:

DIAZEPANE DERIVATIVES OR SALTS THEREOF

Abstract:

Abstract of WO0174791

Compounds exhibiting a blood-anticoagulant effect on the basis of the inhibition of activated blood coagulation factor X and being useful as blood anticoagulants or preventive or therapeutic drugs for diseases caused by thrombus or embolus. As the active ingredient of these drugs are used diazepane derivatives such as 4-[(3-carbamidoylphenylamino)methyl]-
3-[4-(4-methyl-1,4-diazepan-1-yl)benzoylamino]benzoic acid and 3-hydroxy-4'-methoxy-2-{[4-(4-methyl-1,4-diazepan-1-
yl)benzoyl]amino}benzanilide or salts of these derivatives. Data supplied from the esp@cenet database - Worldwide

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(12)特許協力条約に基づいて公開された国際出願

(19) 世界知的所有権機関
国際事務局

(43) 国際公開日
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(30) 優先権データ:
特願2000-096858 2000年3月31日 (31.03.2000) JP

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(81) 指定国 (国内): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL,

[続葉有]

(54) Title: DIAZEPANE DERIVATIVES OR SALTS THEREOF

(54) 発明の名称: ジアゼパン誘導体又はその塩

(57) Abstract: Compounds exhibiting a blood-anticoagulant effect on the basis of the inhibition of activated blood coagulation factor X and being useful as blood anticoagulants or preventive or therapeutic drugs for diseases caused by thrombus or embolus. As the active ingredient of these drugs are used diazepane derivatives such as 4-[(3-carbamidoylphenylamino)methyl]- 3-[4-(4-methyl-1,4-diazepan-1-yl)benzoylamino]benzoic acid and 3-hydroxy-4'-methoxy-2-{[4-(4-methyl-1,4-diazepan-1- yl)benzoyl]amino}benzanilide or salts of these derivatives.

(57) 要約:

活性化血液凝固第X因子の阻害に基づく抗凝固作用を有し、血液凝固抑制剤又は血栓若しくは塞栓によって引きおこされる疾病の予防・治療剤として有用な化合物を提供する。4－［（3－カルバミミドイルフェニルアミノ）メチル］－3－［4-（4-メチル-1、4-ジアゼパン-1-イル）ベンゾイルアミノ］ベンゾイックアシッド 3－ヒドロキシ－4'－メトキシ－2－｛［4－（4－メチル－1，4－ジアゼパン－1－イル）ベンゾイル］アミノ｝ベンズアニリド等のジアゼパン誘導体又はその塩を有効成分とする。

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PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

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明 細 書

ジアゼパン誘導体又はその塩

技術分野

本発明は、医薬、特に活性化血液凝固第Ｘ因子阻害剤として有用な、新規なジアゼパン誘導体又はその塩及びその医薬に関する。

背景技術

近年、生活習慣の欧米化、人口の高齢化等に伴い、心筋梗塞、脳血栓症、末梢動脈血栓症をはじめとする血栓塞栓性疾患は年々増加し、その治療の社会的重要性は益々高まっている。抗凝固療法は、線溶療法及び抗血小板療法とともに血栓症の治療及び予防における内科的治療法の一端を担っている（総合臨床４１：２１４１－２１４５，１９８９）。特に、血栓症の予防においては長期投与に耐えうる安全性と、確実且つ適切な抗凝固活性の発現が必須となる。ワルファリンカリウムは、唯一の経口抗凝固剤として世界中で繁用されているが、その作用機序に基づく特性から抗凝固能のコントロールが難しく（J. Clinical Pharmacology 32,196-209,1992 及び N.Eng.J.Med.324(26)1865-1875,1991）、臨床的には非常に使用しづらい薬剤であり、より有用で使いやすい抗凝固剤の登場が望まれていた。

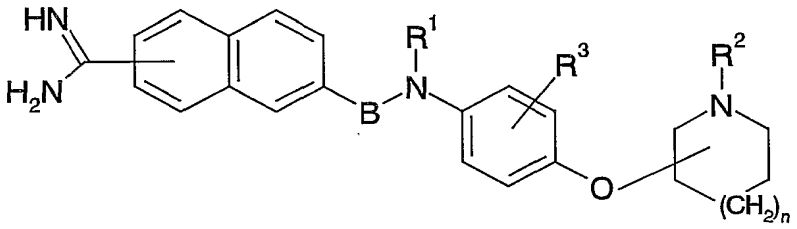
トロンビンは、凝固の最終段階であるフィブリノーゲンのフィブリンへの転化を司るばかりか、血小板の活性化及び凝集にも深く関与し（松尾　理編，Ｔ－ＰＡとＰｒｏ－ＵＫ，学際企画，ｐｐ５－４０　血液凝固，１９８６）、その阻害剤は創薬のターゲットとして長い間抗凝固剤研究の中心にあった。しかしながら、経口投与でのバイオアベイラビリティ（Bioavailability）が低く、安全性面でも問題があり（Biomed. Biochim. Acta 44,1201-1210,1985）、現在のところ経口投与可能なトロンビン阻害剤は上市されていない。

活性化血液凝固第Ｘ因子は外因系及び内因系凝固カスケード反応の合流点に位置するキーエンザイム(Key Enzyme)であり、トロンビンよりも上流に位置するため本因子の阻害はトロンビン阻害よりも効率的で且つ、特異的に凝固系を阻害できる可能性がある（THROMBOSIS RESEARCH(19),339-349,1980）。

活性化血液凝固第Ｘ因子阻害作用を示す化合物としては、アミジノナフチルアルキルベンゼン誘導体又はその塩が知られている（特開平５－２０８９４６号、Thrombosis Haemostasis 71(3), 314-319,1994 及び Thrombosis Haemostasis 72(3),393-

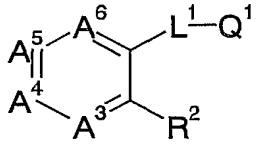
396,1994）。

また、ＷＯ９６／１６９４０号には、下記一般式で示されるアミジノナフチル誘導体又はその塩が、活性化血液凝固第Ｘ因子阻害作用を示す化合物として記載されている（先行技術１）。



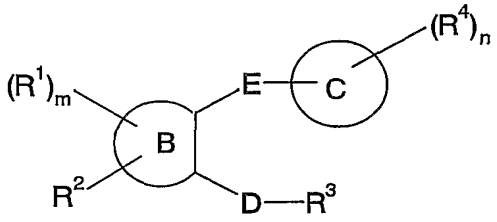
（式中の記号は公報参照。）

また、ＷＯ９９／００１２１号、ＷＯ９９／００１２６号、ＷＯ９９／００１２７号、ＷＯ９９／００１２８号、ＷＯ００／３９１１１号、ＷＯ００／３９１１７号、及びＷＯ００／３９１１８号には、Ｘａ因子阻害剤として下記一般式で示されるフェニレンジアミド化合物等が記載されている（先行技術２）。



（式中の記号は公報参照。）

更に、ＷＯ９９／３２４７７号には、抗凝固剤として下記一般式で示される広範な化合物が記載されている（先行技術３）。

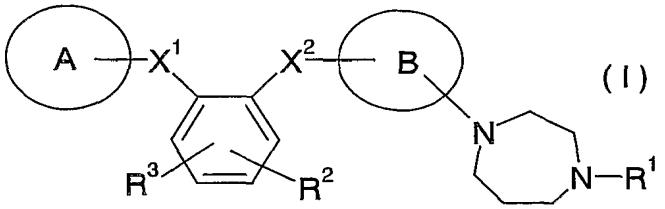


（式中の記号は公報参照。）

発明の開示

本発明者等は、下記一般式（Ｉ）で示されるジアゼパン誘導体又はその塩を創製し、それらが優れた活性化血液凝固第Ｘ因子阻害作用を有し、特に優れた経口活性を有することを見い出した。

すなわち、本発明は、下記一般式（Ｉ）で示されるジアゼパン誘導体又はその塩、並びにそれらを有効成分とする医薬組成物、特に活性化血液凝固第Ｘ因子阻害剤に関する。



（上記式中の記号は、それぞれ以下の意味を有する。

Ａ環、及びＢ環：同一又は異なって１～３個の置換基をそれぞれ有しても良いアリール、又はヘテロアリール、

X^1：-C(=O)-NR^4-、-NR^4-C(=O)-、-NR^4-CH_2-、-O-CH_2-、-CH_2-CH_2-、又は-CH=CH-、

X^2：-C(=O)-NR^5-、又は-NR^5-C(=O)-、

R^1：水素原子、低級アルキル、-低級アルキレン-O-低級アルキル、C_{3-8}シクロアルキル、アリール、ヘテロアリール、-低級アルキレン-C_{3-8}シクロアルキル、-低級アルキレン-アリール、-低級アルキレン-ヘテロアリール、又は-C(=NR^6)-低級アルキル、

R^2：-OH、-O-低級アルキル、-O-低級アルキレン-OH、-O-SO_2-OH、-O-低級アルキレン-COOH、-O-低級アルキレン-COO-低級アルキル、-COOH、-COO-低級アルキル、又はハロゲン原子、

R^3：水素原子、ハロゲン原子、又は低級アルキル、

R^4、R^5、及びR^6：同一又は異なって水素原子、又は低級アルキル）

本発明化合物（Ｉ）は、ジアゼパン-１-イル基を有する点、環状構造を少なくとも４個有する点、ジアゼパンの窒素原子が直接Ｂ環と結合する点等において、先行技術１に記載された化合物とは構造を異にする。また、本発明化合物は、ジアゼパン-１-イル基を有する点において先行技術２と構造を異にする。更に、先行技術３にはジアゼパン-１-イル基を有する化合物は具体的に記載されていない。即ち、本発明化合物（Ｉ）の化学構造上の特徴は、ジアゼパニルアリール又はジアゼパニルヘテロアリールとベンゼン環がアミド結合等を介して結合し、かつ該ベンゼン環がさらにアミド結合等を介してアリール又はヘテロアリールと結合し、かつ該ベンゼン環が-OH、-O-低級アルキル、又はハロゲン原子等を有する点にあ

る。

以下、本発明化合物（Ｉ）につき詳述する。

本明細書中の一般式の定義において「低級」なる用語は、特に断らない限り、炭素数が１～６の直鎖又は分枝状の炭素鎖を意味する。従って、R^1～R^6、及び後記置換基に例示される「低級アルキル」としては、例えばメチル、エチル、プロピル、イソプロピル、ブチル、イソブチル、ｓｅｃ-ブチル、ｔｅｒｔ-ブチル、ペンチル、イソペンチル、ネオペンチル、ｔｅｒｔ-ペンチル、1-メチルブチル、2-メチルブチル、１，２-ジメチルプロピル、ヘキシル、イソヘキシル、１-メチルペンチル、２-メチルペンチル、３-メチルペンチル、１，１-ジメチルブチル、１，２-ジメチルブチル、２，２-ジメチルブチル、１，３-ジメチルブチル、２，３-ジメチルブチル、３，３-ジメチルブチル、１-エチルブチル、２-エチルブチル、１，１，２-トリメチルプロピル、１，２，２-トリメチルプロピル、１-エチル-１-メチルプロピル、１-エチル-２-メチルプロピル等が挙げられる。これらの中では炭素数１～３のものが好ましく、メチル、エチルが特に好ましい。

「低級アルキレン」としては、上述した「低級アルキル」から任意に水素原子１個を除いたC_{1-6}アルキレンを表すが、メチレン、エチレン、プロピレン、イソプロピレンが好ましい。

「アリール」としては、縮合環を含む芳香族炭化水素環を意味し、好ましくは炭素数が６～１４個のアリールが、更に好ましくはフェニル、ナフチル等が挙げられる。

また、「ヘテロアリール」としては、縮合環を含むN、S、Oからなる群より選択された同一又は異なるヘテロ原子を１～４個有する複素環アリールを意味し、具体的にはフリル、チエニル、ピロリル、イミダゾリル、ピラゾリル、イソチアゾリル、イソキサゾリル、トリアゾリル、テトラゾリル、ピリジル、ピリミジニル、ピリダジニル、ピラジニル、インドリル、インダゾリル、インドリジニル、キノリル、イソキノリル、キナゾリニル、キノリジニル、キノキサリニル、シンノリニル、ベンズイミダゾリル、イミダゾピリジル、ベンゾフラニル、ジヒドロベンゾフラニル、ナフチリジニル、１，２-ベンゾイソキサゾリル、ベンゾオキサゾリル、ベンゾチアゾリル、オキサゾロピリジル、イソチアゾロピリジル、ベンゾチエニル等が挙げられるが、これらに限定されるものではない。

「C_{3-8}シクロアルキル」は炭素数３～８個のシクロアルキルを示すが、特にシクロプロ

ピル、シクロブチルが好ましい。

「１～３個の置換基をそれぞれ有しても良いアリール、又はヘテロアリール」の「置換基」としては、置換基を有しても良い低級アルキル、低級アルケニル、低級アルキニル、C_{3-8}シクロアルキル、-O-置換基を有しても良い低級アルキル、ハロゲン原子、$-NH_2$、-NH-低級アルキル、-N-(低級アルキル)$_2$、-C(=NH)-NH_2、-C(=N-OH)-NH_2、-C(=NH)-NH-OH、-C(=NH)-NH-C(=O)-O-低級アルキル、-COOH、-C(=O)-O-置換基を有しても良い低級アルキル、-C(=O)-O-置換基を有しても良いC_{6-14}アリール、-C(=O)-O-置換基を有しても良いヘテロアリール、-CN、$-NO_2$、-OH、-O-CO-置換基を有しても良い低級アルキル、-O-CO-NH_2、-O-CO-NH-低級アルキル、-O-CO-N-(低級アルキル)$_2$、-SH、-C(=O)-NH_2、-C(=O)-NH-(低級アルキル)、-C(=O)-N-(低級アルキル)$_2$等が挙げられる。

ここで「置換基を有しても良い低級アルキル、低級アルケニル、低級アルキニル、C_{3-8}シクロアルキル」、「置換基を有しても良いC_{6-14}アリール」、又は「置換基を有しても良いヘテロアリール」の置換基としては、ハロゲン原子、-COOH、-C(=O)-O-低級アルキル、-OH、$-NH_2$、-NH-低級アルキル、-N-(低級アルキル)$_2$等が挙げられる。

「ハロゲン原子」はフッ素原子、塩素原子、ヨウ素原子、臭素原子が挙げられる。特に塩素原子、及び臭素原子が好ましい。

なお、R^1は低級アルキルが好ましく、特にメチルが好ましい。R^2は、-OHが特に好ましい。R^4～R^6は同一又は異なって水素原子、又は低級アルキルを表すが、水素原子がより好ましい。また、X^1は-C(=O)-NR^4-、-NR^4-C(=O)-、-NR^4-CH_2-、及び-O-CH_2-が好ましく、-C(=O)-NR^4-、及び-NR^4-C(=O)-が特に好ましい。X^2は-C(=O)-NR^5-、又は-NR^5-C(=O)-を表すが、-NR^5-C(=O)-がより好ましい。

A環、及びB環は同一又は異なって、ベンゼン環、ピリジン環、ナフタレン環、チオフェン環、ベンゾフラン環、又はキノリン環が望ましい。ベンゼン環が特に好ましい。

本発明化合物のうち、特に好ましい化合物の具体例は、３－ヒドロキシ－4'－メトキシ－２－｛［4－（4－メチル－１，４－ジアゼパン－１－イル）ベンゾイル］アミノ｝ベンズアニリド、３－ヒドロキシ－N^1－（４－メトキシベンゾイル）－N^2－［4－（4－メチル－１，４－ジアゼパン－１－イル）ベンゾイル］－１，２－フェニレンジアミン、５－クロロ－*N*－（５－クロロ－２－ピリジル）－３－ヒドロキシ－２－｛［４－（4－メチル－

１，４－ジアゼパン－１－イル）ベンゾイル］アミノ｝ベンズアミド、５－クロロ－３－ヒドロキシ－4'－メトキシ－２－｛［４－（４－メチル－１，４－ジアゼパン－１－イル）ベンゾイル］アミノ｝ベンズアニリド、及び５－ブロモ－*N*－（５－クロロ－２－ピリジル）－３－ヒドロキシ－２－｛［４－（４－メチル－１，４－ジアゼパン－１－イル）ベンゾイル］アミノ｝ベンズアミド又はその塩である。

また、本発明化合物は、幾何異性体、互変異性体、光学異性体等の各種の異性体の混合物や単離されたものが含まれる。

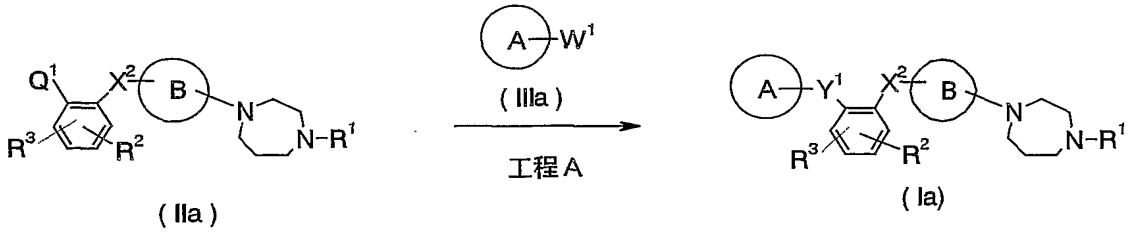
本発明化合物（Ｉ）は、酸付加塩を形成する場合がある。また、置換基の種類によっては塩基との塩を形成する場合もある。かかる塩としては、具体的には、塩酸、臭化水素酸、ヨウ化水素酸、硫酸、硝酸、リン酸等の鉱酸、ギ酸、酢酸、プロピオン酸、シュウ酸、マロン酸、コハク酸、フマール酸、マイレン酸、乳酸、リンゴ酸、酒石酸、クエン酸、メタンスルホン酸、エタンスルホン酸等の有機酸、アスパラギン酸、グルタミン酸等の酸性アミノ酸との酸不加塩、ナトリウム、カリウム、マグネシウム、カルシウム、アルミニウム等無機塩基、メチルアミン、エチルアミン、エタノールアミン等の有機塩基、リジン、オルニチン等の塩基性アミノ酸との塩やアンモニウム塩等が挙げられる。

更に本発明は、化合物（Ｉ）の水和物、製薬学的に許容可能な各種溶媒和物や結晶多形等も含まれる。なお、当然のことながら、本発明は後記実施例に記載された化合物に限定されるものでなく、一般式（Ｉ）で示されるジアゼパン誘導体又はその製薬学的に許容される塩の全てを包含するものである。

なお、本発明化合物には、生体内において代謝されて前記一般式（Ｉ）を有する化合物またはその塩に変換される化合物、いわゆるプロドラッグもすべて含むものである。本発明化合物のプロドラッグを形成する基としては、Ｐｒｏｇ．Ｍｅｄ．５：２１５７－２１６１（１９８５）に記載されている基や、広川書店１９９０年刊「医薬品の開発」第７巻分子設計１６３～１９８頁に記載されている基が挙げられる。

（製造法）

以下に本発明化合物の代表的な製造法を説明する。



（式中、A、B、R^1、R^2、R^3、X^2は前記の意味を有し、Q^1、W^1はQ^1が-NHR^4を意味する場合、W^1は-COOHを意味し、Q^1が-COOHを意味する場合W^1は-NHR^4を意味する。Y^1は-C(=O)-NR^4-、又は-NR^4-C(=O)-を意味する。R^4は前記の意味を有する。）

工程A

化合物(IIa)と化合物(IIIa)の組み合わせからなるカルボン酸とアミンを、好ましくは縮合剤の存在下反応させ、化合物(Ia)を合成する反応である。本反応は常法のアシル化反応に従えばよい。

縮合剤としては、N，N-ジシクロヘキシルカルボジイミド(DCC)、1-エチル-3-［3-（N，N-ジメチルアミノ）プロピル］カルボジイミド、カルボニルジイミダゾール、ジフェニルホスホリルアジド(DPPA)やジエチルホスホリルシアニド等を好適に用いることができる。

また、カルボン酸を対応するカルボン酸の活性誘導体に導いた後にアミンと縮合することも可能である。

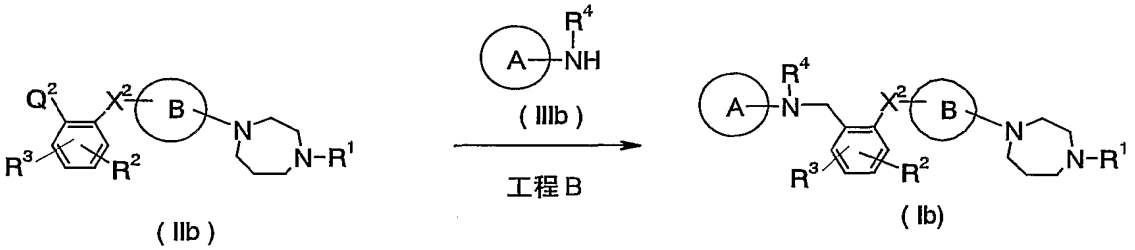
用いるカルボン酸の活性誘導体としてはp-ニトロフェノール等のフェノール系、1-ヒドロキシスクシンイミド、1-ヒドロキシベンゾトリアゾール等のN-ヒドロキシアミン系の化合物と反応させて得られる活性エステル、炭酸モノアルキルエステル、又は有機酸と反応させて得られる混合酸無水物や塩化ジフェニルホスホリル、N-メチルモルホリンとを反応させて得られるリン酸系混合酸無水物；エステルをヒドラジン、亜硝酸アルキルと反応させて得られる酸アジド；酸クロライド、酸ブロマイド等の酸ハライド、対称型酸無水物等が挙げられる。通常、前記反応は、溶媒中において、冷却～室温下に行うが、アシル化反応の種類により、無水条件下に実施しなければならない場合もある。

溶媒としては、反応に関与しない溶媒、例えば水、エタノール、メタノール、ジメチルホルムアミド、ジオキサン、テトラヒドロフラン、エーテル、ジクロロエタン、ジクロロメタン、クロロホルム、四塩化炭素、ジメトキシメタン、ジメトキシエタン、酢酸エチル、ベン

ゼン、アセトニトリル、ジメチルスルホキシド等やこれらの混合溶媒等を用いることができるが、適用する方法に応じ適宜選択するのが好ましい。

また、適用する方法によっては、炭酸ナトリウム、炭酸カリウム、ナトリウムエトキシド、カリウムｔ-ブトキシド、１、８-ジアザビシクロ［５．４．０］ウンデス-７-エン(ＤＢＵ)、Ｎ-メチルモルホリン、トリエチルアミン、トリメチルアミン、ピリジン、水素化ナトリウム、ブチルリチウム、ソディウムアミド等の塩基の存在下で又はこれら塩基を溶媒として反応させることにより、反応が円滑に進行する場合がある。

またここに記載の反応以外でも、アミド結合を形成する反応であればいずれの方法も用いることができる。



(式中、Ａ、Ｂ、R^1、R^2、R^3、R^4、X^2は前記の意味を有し、Q^2は-ＣＨＯ又は、-CH_2-脱離基を意味する。脱離基としては、ハロゲン原子、-Ｏ-(SO_2)-アルキル、-Ｏ-(SO_2)-アリール等が挙げられる。)

工程Ｂ

化合物(IIb)と化合物(IIIb)の組み合わせからなるアルデヒドとアミン、又は-CH_2-脱離基を持つ化合物とアミンを、縮合させ化合物(Ib)を合成する反応である。

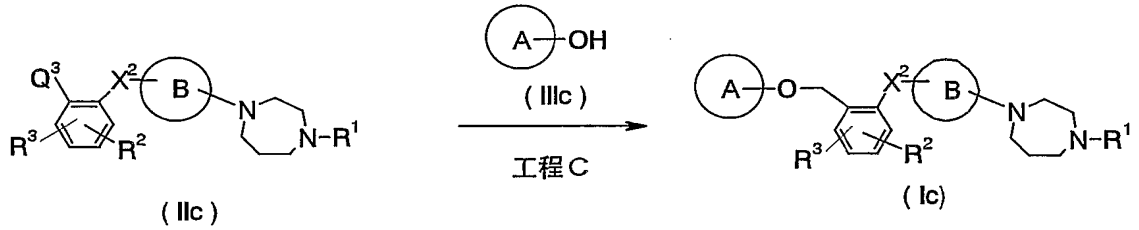
アルデヒドとアミンの組み合わせの場合、本反応は、還元剤の存在下常法の還元的アミノ化反応に従えばよい。

還元剤としては、例えば水素化ホウ素ナトリウム、水素化シアノホウ素ナトリウム、トリアセトキシ水素化ホウ素ナトリウム、ボラン-トリメチルアミン錯体等を好適に用いることができる。また、パラジウム-炭素、酸化白金等の触媒存在下、常圧～加圧下、接触水素添加を行っても良い。本反応は、前記反応に関与しない溶媒中、冷却下～加熱下行われる。また、適用する方法によっては、酢酸、トルエンスルホン酸、硫酸等の酸の存在下又はこれらを溶媒として反応させることにより反応が円滑に進行する場合がある。

-CH_2-脱離基を持つ化合物とアミンの組み合わせの場合、本反応は、常法のＮ-アルキル化反応に従えばよい。

本反応は、前記反応に関与しない溶媒中、冷却下～加熱下行われる。また、適用する方法によっては、前記塩基の存在下、又はこれら塩基を溶媒として反応させることにより、反応が円滑に進行する場合がある。

またここに記載の反応以外でも、$-NR^4-CH_2-$の結合を形成する反応であればいずれの方法も用いることができる。



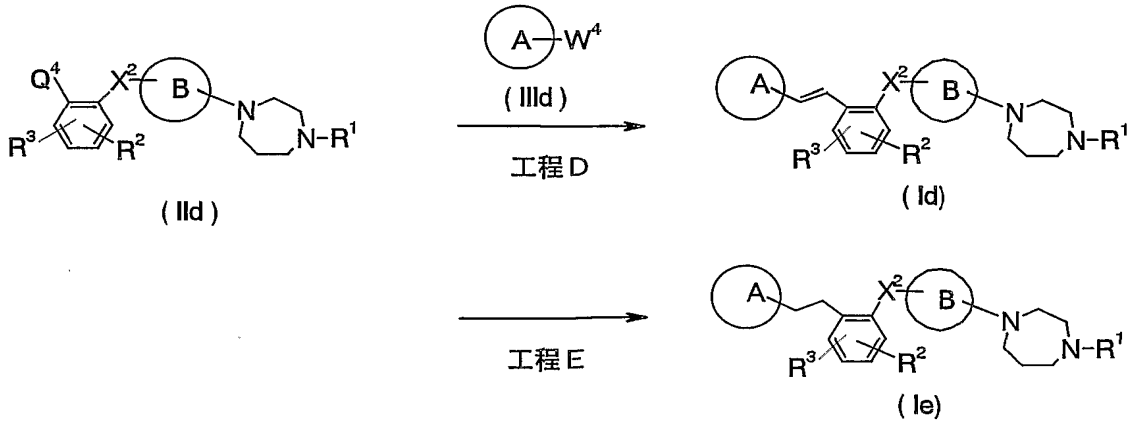
(式中、A、B、R^1、R^2、R^3、X^2は前記の意味を有し、Q^3は、$-CH_2-$脱離基を意味する。脱離基としては、ハロゲン原子、$-O-(SO_2)-$アルキル、$-O-(SO_2)-$アリール等が挙げられる。)

工程C

化合物(IIc)と化合物(IIIc)の組み合わせからなる$-CH_2-$脱離基を持つ化合物とアルコールを縮合させ、化合物(Ic)を合成する反応である。本反応は、常法のO-アルキル化反応に従えばよい。

本反応は、前記反応に関与しない溶媒中、冷却下～加熱下行われる。また、適用する方法によっては、前記塩基の存在下、又はこれら塩基を溶媒として反応させることにより、反応が円滑に進行する場合がある。

またここに記載の反応以外でも、エーテル結合を形成する反応であればいずれの方法も用いることができる。



(式中、A、B、R^1、R^2、R^3、X^2は前記の意味を有し、Q^4、W^4はQ^4が-CHOを意味

する場合、W^4は-CH_2-$P^+Ph_3Br^-$等のホスホニウム塩、-CH_2-P(=O)(-OEt)$_2$等の亜リン酸ジエステル、又は-CH_2-P(=O)(-Ph)$_2$等のホスフィンオキシドを意味し、W^4が-CHOを意味する場合Q^4はCH_2-$P^+Ph_3Br^-$等のホスホニウム塩、-CH_2-P(=O)(-OEt)$_2$等の亜リン酸ジエステル、又は-CH_2-P(=O)(-Ph)$_2$等のホスフィンオキシドを意味する。)

工程D

化合物(IId)と化合物(IIId)の組み合わせからなるアルデヒドとホスホニウム塩、亜リン酸ジエステル、またはホスフィンオキシドを、前記塩基の存在下反応させ、化合物(Id)を合成する反応である。本反応は常法のWittig反応、またはWittig-Horner反応に従えばよい。

本反応は、前記反応に関与しない溶媒中、冷却下～加熱下行われる。適用する方法によっては、中間体イリドを単離した後、アルデヒドと反応することもできる。

またここに記載の反応以外でも、炭素と炭素の２重結合を形成する反応であればいずれの方法も用いることができる。

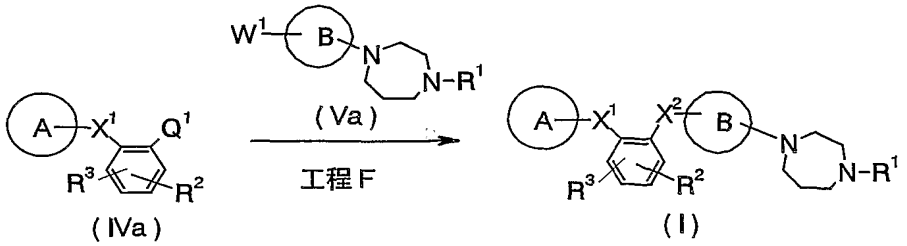
工程E

化合物(Id)を還元反応により化合物(Ie)を合成する反応である。本反応は触媒を用いる常法の水素添加反応に従えばよい。

本反応は、水素雰囲気下、前記反応に関与しない溶媒中、冷却下～加熱下行われる。適用する方法によっては加圧下行われる。用いられる触媒としては、パラジウム-炭素(Pd-C)、酸化白金、ラネーニッケル、クロロトリフェニルホスフィンロジウム(Wilkinson触媒)、ホウ素化ニッケル等が挙げられる。また、水素雰囲気下で行う代わりに、蟻酸アンモニウム、ホスフィン酸ナトリウム、ヒドラジン等を水素源として用いることもできる。

またここに記載の反応以外でも、２重結合を還元する反応であればいずれの方法も用いることができる。

また、化合物(Id)を経由しなくても、-CH_2-CH_2-結合を形成する反応であればいずれの方法も用いることができる。



（式中、A、B、R^1、R^2、R^3、X^1、X^2、Q^1、W^1は前記の意味を有する。）

工程F

化合物(IVa)と化合物(Va)の組み合わせからなるカルボン酸とアミンを反応させ化合物(I)を合成する反応である。本反応は工程Aと同様な方法で実施される。

本発明化合物(I)中R^1が水素の化合物は、本発明化合物(I)中R^1がベンジルの化合物を用いて、前記水素添加反応等を行うことにより得ることもできる。

また、本発明化合物(I)中R^1が水素原子の化合物を用いて、前記常法の還元的アミノ化、又はN-アルキル化等を行うことにより本発明化合物(I)中R^1が水素原子以外の化合物を得ることもできる。

また、本発明化合物(I)中R^2が-OHの化合物は、その水酸基をフェノールの保護基で保護した化合物を合成した後、その保護基を切断するのに適した方法で切断することより得ることもできる。ここでフェノールの保護基としては、通常、フェノールの保護に用いられる基であれば特に制限はなく、例えば置換されてもよい低級アルキル、アラルキル、トリ低級アルキルシリル、低級アルキルカルボニル、低級アルキルオキシカルボニル、スルホニル等が挙げられる。「アラルキル」としては前記アルキルの水素原子がアリールに置換された基を意味し、具体的にはベンジル、フェニルエチル等が挙げられる。

本発明化合物(I)中R^2が-OHの化合物を用いて前記常法の-O-アルキル化等を行うことによりR^2が-O-低級アルキル、-O-低級アルキレン-OH、-O-低級アルキレン-COOH、-O-低級アルキレン-COO-低級アルキルの化合物を得ることもできる。また、本発明化合物(I)中R^2が-OHの化合物をトリメチルアミン-サルファートリオキサイド　錯体等を用い、スルホン酸化することによりR^2が-O-SO_2-OHの化合物を得ることができる。更にR^2にエステル基が存在する場合には、塩酸水溶液等の酸性条件下、又は水酸化ナトリウム水溶液等の塩基性条件下加水分解することによりR^2にカルボキシル基が存在する化合物を得ることができる。

本発明化合物(I)中A環にニトリル基を有する化合物を用いて本発明化合物(I)中A環にヒドロキシアミジノ基、又はアミジノ基を有する化合物を得ることもできる。

本発明化合物(I)中A環にヒドロキシアミジノ基を有する化合物の合成法としては、本発明化合物(I)中A環にニトリル基を有する化合物とヒドロキシルアミンを反応させることに

より行うことができる。本反応は、前記反応に関与しない溶媒中、冷却下～加熱下行われる。また、適用する方法によっては、前記塩基の存在下、又はこれら塩基を溶媒として反応させることにより、反応が円滑に進行する場合がある。

本発明化合物(I)中A環にアミジノ基を有する化合物の合成法としては以下の(ｉ)～(iv)に示す方法が挙げられる。

(ｉ)ニトリルをイミデートに変換した後、アミンと縮合させる方法：

本発明化合物(I)中A環にニトリル基を有する化合物に塩酸ガス存在下、メタノールやエタノール等のアルコールを－４０℃～０℃で作用させ、イミデートに変換した後、アンモニア、炭酸アンモニウム、塩化アンモニウム、酢酸アンモニウム等のアミン又はアミン塩を反応させる。溶媒としては、前記反応に関与しない溶媒を用いることができる。

(ii)ニトリルを、チオアミドを経由してチオイミデートに変換し、アミンと縮合させる方法：

本発明化合物(I)中A環にニトリル基を有する化合物にメチルアミン、トリエチルアミン、ピリジン、ピコリン等の有機塩基の存在下で硫化水素を作用させ、又は本発明化合物(I)中A環にニトリル基を有する化合物に塩化水素の存在下でジチオリン酸 o,o-ジエチルを作用させ、チオアミド体に誘導する。

次いで、前記チオアミド体にヨウ化メチル、ヨウ化エチル等の低級アルキルハロゲン化物を反応させ、チオイミデート体に変換し、アンモニア、炭酸アンモニウム、塩化アンモニウム、酢酸アンモニウム等のアミン又はアミン塩を反応させる。溶媒としては、前記反応に関与しない溶媒を用いることができる。

(iii)ニトリルにアミン、アミン塩、金属アミド、グルニャール試薬を直接付加させる方法：

本発明化合物(I)中A環にニトリル基を有する化合物にアンモニア、塩化アンモニウムとアンモニア、チオシアン酸アンモニウム、チオシアン酸アルキルアンモニウム、$NaNH_2$、$(CH_3)_2NMgBr$等の試薬を付加させる。溶媒としては、前記反応に関与しない溶媒を用いることができる。また、無溶媒で反応を行うこともできる。

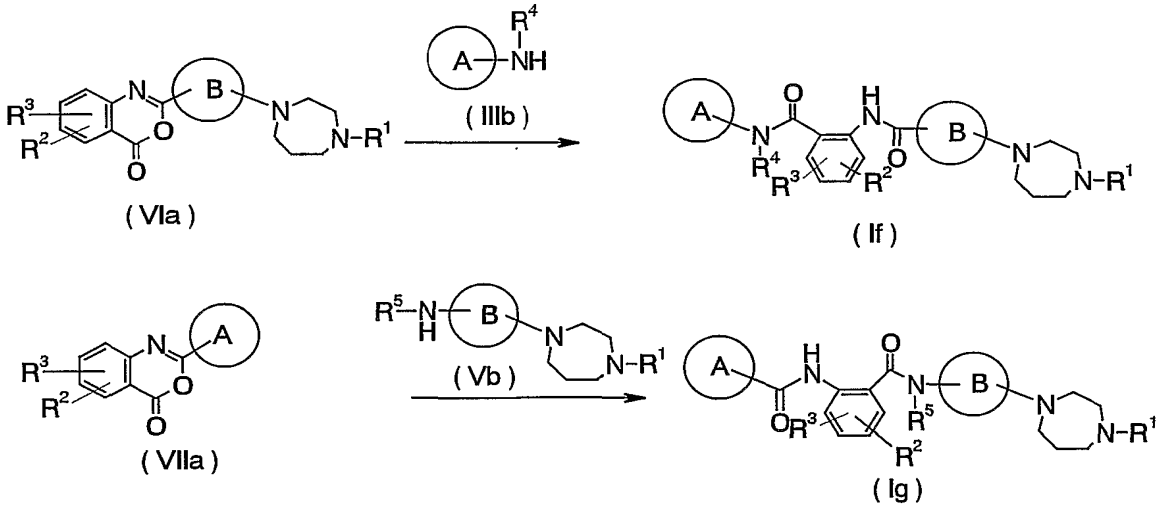
(iv)ヒドロキシアミジノ基を還元する方法：

本発明化合物(I)中A環にヒドロキシアミジノ基を有する化合物を用いて、直接前記水素添加反応を行うか、又は、無水酢酸又は無水トリフルオロ酢酸を、酢酸又はトリフルオロ酢

酸等を溶媒として作用させた後、前記水素添加反応を行うことにより、ヒドロキシアミジノ基を還元することができる。

また、ここに記載の反応以外でも、アミジノ基を形成する反応であればいずれの方法も用いることができる。

また、一般式(I)で示される化合物は、その他公知のアルキル化、アシル化、酸化、還元、加水分解等、当業者が通常採用し得る工程を任意に組み合わせることにより製造することができる。更に、以下の反応式に示す方法は、一般式(I)で示される化合物を合成する為に特に有効である。

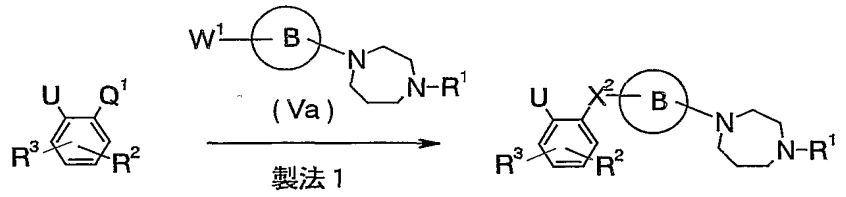


(式中、A、B、R^1、R^2、R^3、R^4、及びR^5は前記の意味を有する)

化合物(VIa)とアミン(IIIb)又は、化合物(VIIa)とアミン(Vb)を反応しアミド結合を形成させ、化合物(If)又は、化合物(Ig)を得る反応であり、前記不活性溶媒中、室温～加温下行われる。また、適用する方法によっては、N-メチルモルホリン、トリエチルアミン、トリメチルアミン、ピリジン、水素化ナトリウム、カリウム-t-ブトキシド、ブチルリチウム、ソディウムアミド等の塩基の存在下で又はこれら塩基を溶媒として反応することにより、反応が円滑に進行する場合がある。

(原料化合物の製法)

以下、本発明化合物(I)の原料化合物について代表的な製造法を説明する。



(VIIIa) (IIe)

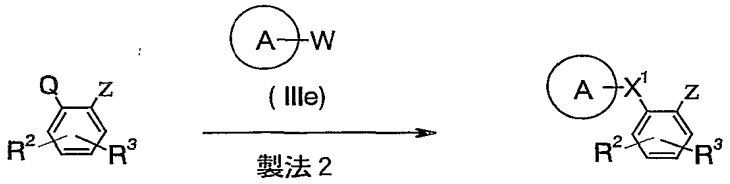
(式中、B、R^1、R^2、R^3、Q^1、W^1、及びX^2は前記の意味を有し、Uは-COOH、-NHR^5、-CH_2-脱離基、-CHO、-CH_2-$P^+Ph_3Br^-$等のホスホニウム塩、-CH_2-P(=O)(-OEt)$_2$等の亜リン酸ジエステル、又は-CH_2-P(=O)(-Ph)$_2$等のホスフィンオキシドを意味する。R^5は前記の意味を有する。)

製法1

化合物(VIIIa)と化合物(Va)の組み合わせからなるカルボン酸とアミンを縮合しアミド結合を形成する反応である。本反応は、前記工程Aと同様にして実施される。

また、化合物(IIe)中Uが-CH_2-脱離基を意味する場合は4-メチルモルホリン N-オキシド等を用いる酸化反応によりUが-CHOの化合物を得ることができ、トリフェニルホスフィン等の有機リン化合物と反応させることによりUが-CH_2-$P^+Ph_3Br^-$等のホスホニウム塩の化合物を得ることができる。

また、一般式(IIe)で示される化合物は、その他公知のアルキル化、アシル化、酸化、還元、加水分解等、当業者が通常採用し得る工程を任意に組み合わせることにより製造することができる。例えば、Uに相当する部位に-NO_2を有する化合物を得た後、前記水素添加反応等の還元反応を行い、UがNH_2の化合物を得ることができる。また、Uに相当する部位にエステル基を有する化合物を得た後、塩酸水溶液等を用いるの酸性条件、水酸化ナトリウム等を用いるアルカリ性条件で加水分解を行い、Uが-COOHの化合物を得ることができる。更に、Uに相当する部位にt-ブトキシカルボニル基やベンジル基等で保護されたアミノ基を有する化合物を用いて、トリフルオロ酢酸等を用いる酸性条件、及び前記水素添加反応等の還元条件など、それぞれの保護基を切断するのに適した方法で切断することによりUが-NHR^{5}の化合物を得ることができる。



(VIIIb) (IVb)

(式中、A、R^2、R^3及びX^1は前記の意味を有する。Zは-COOH、$-NHR^5$を意味する。Q、WはQがQ^1を意味する場合、WはW^1を意味し、QがQ^2を意味する場合Wは$-NHR^4$を意味し、QがQ^3を意味する場合Wは-OHを意味し、又QがQ^4を意味する場合WはW^4を意味する。Q^1、Q^2、Q^3、Q^4、W^1、W^4、R^4は前記の意味を有する。)

製法2

QがQ^1を、WがW^1を意味する場合、化合物(VIIIb)と化合物(IIIe)の組み合わせからなるカルボン酸とアミンを反応させ、化合物(IVb)を合成する反応である。本反応は工程Aと同様な方法で実施できる。

QがQ^2を、Wが$-NHR^4$意味する場合、化合物(VIIIb)と化合物(IIIe)の組み合わせからなるアルデヒドとアミン、又は$-CH_2$-脱離基を持つ化合物とアミンを、縮合させ化合物(IVb)を合成する反応である。本反応は工程Bと同様な方法で実施できる。

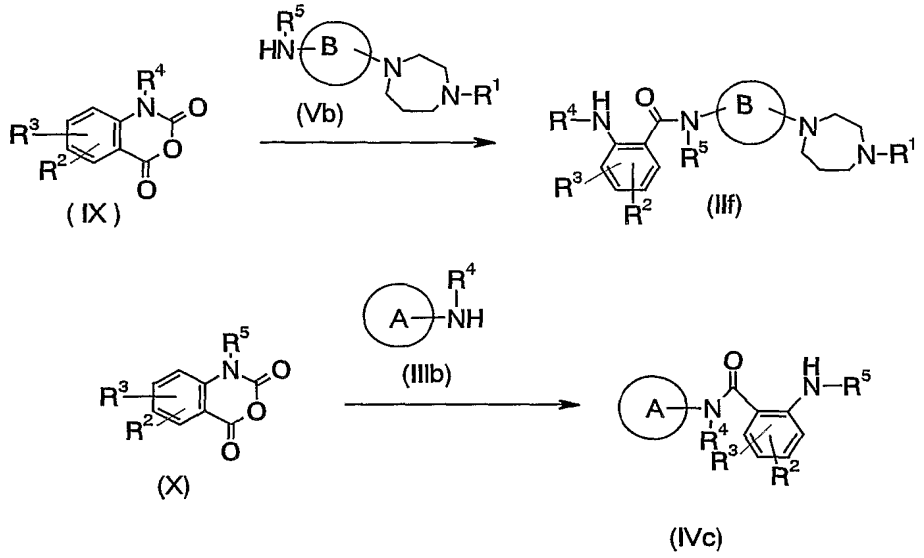
QがQ^3を、Wが-OH意味する場合、化合物(VIIIb)と化合物(IIIe)の組み合わせからなる$-CH_2$-脱離基を持つ化合物とアルコールを、縮合させ化合物(IVb)を合成する反応である。本反応は工程Cと同様な方法で実施できる。

QがQ^4を、WがW^4意味する場合、化合物(VIIIb)と化合物(IIIe)の組み合わせからなるアルデヒドとホスホニウム塩、亜リン酸ジエステル、またはホスフィンオキシドを縮合させ化合物(IVb)を合成する反応である。本反応は工程Dと同様な方法で実施できる。

また、一般式(IVb)で示される化合物は、その他公知のアルキル化、アシル化、酸化、還元、加水分解等、当業者が通常採用し得る工程を任意に組み合わせることにより製造することができる。例えば、Zに相当する部位に$-NO_2$を有する化合物を得た後、前記水素添加反応等の還元反応を行い、Zが$-NH_2$の化合物を得ることができる。また、Zに相当する部位にエステル基を有する化合物を得た後、塩酸水溶液等を用いるの酸性条件、水酸化ナトリウム等を用いるアルカリ性条件で加水分解を行い、Zが-COOHの化合物を得ることができる。更に、Zに相当する部位にt-ブトキシカルボニル基やベンジル基等で保護されたアミノ基を有する化合物を用いて、トリフルオロ酢酸等を用いるの酸性条件、及び前記水素添加

反応等の還元条件など、それぞれの保護基を切断するのに適した方法で切断することにより、ZがーNHR^{5}の化合物を得ることができる。

また、以下の反応式に示す方法は、一般式(IIf)、(IVc)で示される化合物を合成する為に特に有効である。



(式中、A、B、R^1、R^2、R^3、R^4、及びR^{5}は前記の意味を有する)

化合物(IX)とアミン(Vb)、又は化合物(X)とアミン(IIIb)を反応させアミド結合を形成し、化合物(IIf)、又は化合物(IVc)を得る反応であり、前記不活性溶媒中、室温～加温下行われる。また、適用する方法によっては、N-メチルモルホリン、トリエチルアミン、トリメチルアミン、ピリジン、水素化ナトリウム、カリウム-t-ブトキシド、ブチルリチウム、ソディウムアミド等の塩基の存在下又はこれら塩基を溶媒として反応することにより、反応が円滑に進行する場合がある。

この様にして製造された本発明化合物は、公知の方法、例えば、抽出、沈澱、分画クロマトグラフィー、分別結晶化、再結晶等により単離、精製することができる。また、本発明化合物の塩には、通常の造塩反応により導くことができる。

また、本発明化合物が不斉炭素を有する場合には光学異性体が存在する。これらの光学異性体は適切な塩と再結晶する分別結晶化やカラムクロマトグラフィー等の常法により分割することができる。

産業上の利用可能性

本発明化合物は、活性化血液凝固第X因子を特異的に阻害し、強力な抗凝固作用を有する。

従って、血液凝固抑制剤、又は血栓若しくは塞栓によって引きおこされる疾病の予防・治療剤として有用である。

上記疾病として脳梗塞、脳血栓、脳塞栓、一過性脳虚血発作（ＴＩＡ）、くも膜下出血（血管れん縮）等の脳血管障害における疾病、急性及び慢性心筋梗塞、不安定狭心症、冠動脈血栓溶解等の虚血性心疾患における疾病、肺梗塞、肺塞栓等の肺血管障害における疾病、更に末梢動脈閉塞症、深部静脈血栓症、汎発性血管内凝固症候群、人工血管術後及び人工弁置換後の血栓形成症、冠動脈バイパス術後における再閉塞及び再狭窄、ＰＴＣＡ（Percutaneous transluminal coronary angioplasty）、又はＰＴＣＲ(Percutaneous transluminal coronary recanalization）術後における再閉塞及び再狭窄、体外循環時の血栓形成症等の各種血管障害における疾病が挙げられる。

また、活性化血液凝固第Ｘ因子阻害作用を有する化合物について、インフルエンザウイルスへの増殖阻害活性に基づく、インフルエンザウイルスの感染予防・治療剤としての可能性が示唆されているので（特開平６－２２７９７１号）本発明化合物も同様の効果が期待される。

本発明の化合物の優れた活性化血液凝固第Ｘ因子阻害活性は、以下に示す試験方法により確認された。

１）ヒト活性化血液凝固第Ｘ因子(human factor Xa)凝固時間測定試験

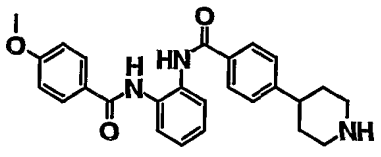
ヒト血漿 90 μｌに薬剤または生理食塩水 10 μｌおよびhuman factor Xa (Enzyme Research Labs) 50 μｌを加え、37 ℃で 3 分間インキュベートした後、予め３７℃に加温した 20 mM の $CaCl_2$ を 100 μｌ添加して凝固計（Amelung 社：KC10）にて凝固するまでの時間を測定した。ヒト血漿は健常人（6 人）の肘静脈より 3.8 %の sodium citrate が 5 ml 入ったシリンジで血液 45 ml を採血し、 4 ℃・3000 rpm・15 分の遠心により分離した血漿をプールし凍結保存したものを使用した。human factor Xa は生理食塩水(コントロール)を添加したときの凝固時間が約 30～40 秒になるような濃度を選択した。CT_2 値(コントロールの凝固時間を 2 倍に延長する濃度)は、凝固時間のコントロールに対する相対値(fold)と薬剤濃度をプロットし、直線回帰することで求めた。この結果を下記表１に示す。

２）ウシトロンビン凝固時間測定試験

ヒト血漿 50 μl に薬剤または生理食塩水 50 μl を加え、37 ℃で 3 分間インキュベートした後、予め３７℃に加温した thrombin (Thrombin(ウシ由来) 500units 持田製薬) 50 μl 添加して、凝固計 (Amelung 社：KC10) にて凝固するまでの時間を測定した。ヒト血漿は健常人 (6 人) の肘静脈より 3.8 %の sodium citrate が 5 ml 入ったシリンジで血液 45 ml を採血し、 4 ℃・3000 rpm・15 分の遠心により分離した血漿をプールし凍結保存したものを使用した。thrombin は生理食塩水(コントロール)を添加したときの凝固時間が約 20 秒になるような濃度を選択した。CT_2値(コントロールの凝固時間を 2 倍に延長する濃度)は、凝固時間のコントロールに対する相対値(fold)と薬剤濃度をプロットし、直線回帰することで求めた。この結果を下記表１に示す。

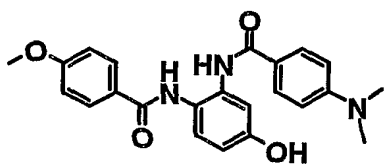
表１

	化合物	ヒト活性化血液凝固第Ｘ因子凝固時間測定試験（CT_2）（μM）	ウシトロンビン凝固時間測定試験（CT_2）（μM）
実施例化合物	実施例５	０．１０	＞１００
	実施例９	１．７１	＞１００
	実施例１１	１．３３	＞１００
	実施例３２	１．４１	＞１００
	実施例３９	１．５３	＞１００
対照化合物	対照１	１７．０	＞１００
	対照２	１１．３	－



(対照１)

(WO99/00121号の実施例42)



(対照２)

(WO99/00121号の実施例198)

３）合成基質法による酵素阻害測定試験

96 穴マイクロプレートに反応緩衝液 (pH 8.4) 80 μl、化合物溶液 15 μl、合成基質 S-

2222 (Chromogenix) 2 mM 30 μl を添加し、ヒト活性化血液凝固第X因子(factor Xa Enzyme Research Labs) 0.025U/ml 25 μl を加え、10分間37℃で反応させた後、405 nm の吸光度変化を Bio-Rad 社モデル 3550 で測定し、IC_{50} を算出した。実施例1の化合物は 10 nM 以下の IC_{50} を示した。

以上1）、2）、及び3）の測定の結果、本発明化合物はヒト活性化血液凝固第X因子を特異的に阻害し、かつ、強い抗血液凝固作用を示すことが確認された。例えば、本発明の実施例５、９、１１、３２、及び３９に示される化合物は、ＷＯ９９／００１２１号の実施例４２（対照１）、及び同実施例１９８（対照２）と比較して、明らかに低濃度で凝固時間を延長し、優れた抗血液凝固作用を示すことが確認された。

4）マウスを用いたex vivoでの凝固時間測定試験（経口投与）

12時間以上絶食した雄性ICRマウス(20～30g、日本SLC社)に対し、0.5%メチルセルロースにて溶解もしくは懸濁した薬剤を経口ゾンデを用いて強制経口投与し(100mg/kg)、30分後および2時間後にジエチルエーテル麻酔下で、下大静脈より3.8%のsodium citrateが100μl入ったシリンジで0.9ml採血し、3000rpm・10分の遠心処理により血漿を分離した。この血漿を用いて以下a)及びb)の方法に従い、外因系凝固時間(PT)及び内因系凝固時間(APTT)の測定を行った。

a)外因系凝固時間(PT)

オーソ ブレーン トロンボプラスチン(54mg/vial、凍結乾燥製剤、オーソ・クリニカル・ダイアグノスティックス社)をMilli-Q水2.5mlに溶解し37℃にて予備加温した。上記血漿50μlを37℃にて1分間加温し、上記トロンボプラスチン溶液50μlを添加し凝固時間の測定を行った。凝固時間の測定にはAmelung社KC10Aを使用した。

b)内因系凝固時間(APTT)

上記血漿50μlにヘモライアンス トロンボシルＩ（ダイアヤトロン社）50μlを加え37℃にて3分間加温し、あらかじめ37℃にて予備加温した20mMの$CaCl_2$溶液50μlを添加し凝固時間の測定を行った。凝固時間の測定にはAmelung社KC10Aを使用した。

なお、抗凝固作用の用量依存性及び経時変化に関しても、投与用量あるいは採血時間を変更し同様の方法にて検討した。

5）カニクイザルを用いたex vivoでの凝固時間測定法（経口投与）

12時間以上絶食した雄性カニクイザル（体重4 kg前後）に対し、薬剤投与前の採血後、0.5%メチルセルロースに溶解（懸濁）した薬剤（5 mg/ml）を経口ゾンデを用いて2 ml/kg強制経口投与し(10 mg/kg)、1、 2、 4、 6、 8時間後、大腿静脈より3.8%クエン酸ナトリウム1/10容にて2 ml採血し、3000 rpm 10分の遠心処理により血漿を分離した。この血漿を用いて上記 a)及び b)の方法に従い外因系凝固時間(PT)及び内因系凝固時間(APTT)の測定を行った。実験は無麻酔条件下で行った。

４）、及び５）の試験の結果、本発明化合物は経口投与においても凝固時間の延長作用が認められた。実施例３に示される化合物は４） ５）両方の試験においてＰＴ、ＡＰＴＴ共にコントロール（薬剤未投与の血漿）に比べ２倍以上の凝固時間延長作用を示した。

一般式（Ｉ）で示される本発明化合物やその製薬学的に許容される塩の１種又は２種以上を有効成分として含有する医薬組成物は、通常用いられる製剤用の担体や賦形剤、その他の添加剤を用いて、錠剤、散剤、細粒剤、顆粒剤、カプセル剤、丸剤、液剤、注射剤、坐剤、軟膏、貼付剤等に調製され、経口的又は非経口的に投与される。

本発明化合物のヒトに対する臨床投与量は適用される患者の症状、体重、年齢や性別等を考慮して適宜決定されるが、通常成人１日当たり経口で０．１～５００ｍｇ、非経口で０．０１～１００ｍｇであり、これを１回あるいは数回に分けて投与する。投与量は種々の条件で変動するので、上記投与量範囲より少ない量で十分な場合もある。

本発明による経口投与のための固体組成物としては、錠剤、散剤、顆粒剤等が用いられる。このような固体組成物においては、一つ又はそれ以上の活性物質が、少なくとも一つの不活性な希釈剤、例えば乳糖、マンニトール、ブドウ糖、ヒドロキシプロピルセルロース、微結晶セルロース、デンプン、ポリビニルピロリドン、メタケイ酸アルミン酸マグネシウムと混合される。組成物は、常法に従って、不活性な希釈剤以外の添加剤、例えばステアリン酸マグネシウムのような潤滑剤や繊維素グリコール酸カルシウムのような崩壊剤、ラクトースのような安定化剤、グルタミン酸又はアスパラギン酸のような可溶化剤又は溶解補助剤を含有していてもよい。錠剤又は丸剤は必要によりショ糖、ゼラチン、ヒドロキシプロピルセルロース、ヒドロキシプロピルメチルセルロースフタレート等の胃溶性あるいは腸溶性物質のフィルムで被膜してもよい。

経口投与のための液体組成物は、薬剤的に許容される乳濁剤、溶液剤、懸濁剤、シロップ剤、エリキシル剤等を含み、一般的に用いられる不活性な希釈剤、例えば精製水、エチルアルコールを含む。この組成物は不活性な希釈剤以外に可溶化剤、溶解補助剤、湿潤剤、懸濁剤のような補助剤、甘味剤、風味剤、芳香剤、防腐剤を含有していてもよい。

非経口投与のための注射剤としては、無菌の水性又は非水性の溶液剤、懸濁剤、乳濁剤を包含する。水性の溶液剤、懸濁剤の希釈剤としては、例えば注射剤用蒸留水及び生理食塩水が含まれる。非水溶性の溶液剤、懸濁剤の希釈剤としては、例えばプロピレングリコール、ポリエチレングリコール、オリーブ油のような植物油、エチルアルコールのようなアルコール類、ポリソルベート８０（商品名）等がある。

このような組成物は、更に等張化剤、防腐剤、湿潤剤、乳化剤、分散剤、安定化剤（例えば、ラクトース）、可溶化剤又は溶解補助剤のような添加剤を含んでもよい。これらは例えばバクテリア保留フィルターを通す濾過、殺菌剤の配合又は照射によって無菌化される。これらは又無菌の固体組成物を製造し、使用前に無菌水又は無菌の注射用溶媒に溶解して使用することもできる。

発明を実施するための最良の形態

以下、本発明化合物の製造例を挙げ、本発明化合物の製造方法を具体的に説明する。なお、本発明化合物の原料化合物には新規な化合物も含まれており、これらの化合物の製造方法を参考例として説明する。

参考例１

エチル　４－ブロモメチル－３－ニトロベンゾアート２６．００ｇをアセトニトリル９０ｍｌに溶解し、３－アミノベンゾニトリル７．９７ｇ及び、炭酸カリウム１２．４４ｇを加え、７０℃で３時間攪拌した。室温まで冷却し、濾過後、母液を減圧下濃縮した。得られた残渣に酢酸エチルを加え、１規定塩酸水溶液、飽和炭酸水素ナトリウム水溶液で洗った後、無水硫酸マグネシウムで乾燥後、減圧下濃縮した。得られた残渣を、ヘキサン：酢酸エチル（８０：２０～７５：２５）を溶出溶媒とするシリカゲルカラムクロマトグラフィーにて精製し、エチル　４－［（３－シアノフェニルアミノ）メチル］－３－ニトロベンゾアート１２．０６ｇを得た。

参考例２

エチル　４－［（３－シアノフェニルアミノ）メチル］－３－ニトロベンゾアート５．７９ｇをエタノール５０ｍｌに溶解し、精製水５０ｍｌ、塩化アンモニウム０．９６ｇ、鉄粉末４．９７ｇを加え４０分間加熱環流した。反応液をセライト濾過し、減圧下濃縮した。得られた残渣に酢酸エチルを加え、飽和炭酸水素ナトリウム水溶液と、飽和食塩水で洗い、無水硫酸マグネシウムで乾燥後、減圧下濃縮、乾燥しエチル　３－アミノ－４－［（３－シアノフェニルアミノ）メチル］ベンゾアート５．７１ｇを得た。

参考例３

エチル　４－ブロモメチル－３－ニトロベンゾアート46.11gをアセトニトリル500mlに溶解し、これに4-メチルモルホリン－*N*－オキシド20g加え室温にて80分攪拌した。反応液を減圧濃縮し、水を加えクロロホルムにて抽出した。この有機層を飽和食塩水で洗浄し、硫酸マグネシウムで乾燥し、減圧濃縮した。得られた残渣をヘキサン：酢酸エチル（４：１）を溶出溶媒とするシリカゲルカラムクロマトグラフィーにて精製し、エチル　４－ホルミル－３－ニトロベンゾアート10.723g得た。

参考例４

エチル　４－ホルミル－３－ニトロベンゾアート5.81gをトルエン70mlに溶解し、これに1,8－ジアザビシクロ[5.4.0]－ウンデセ－７－エン2.1mlを加え、80度にて1時間攪拌した。これに３－[（１，１，１，－トリフェニルフォスソニオ）メチル]ベンゾニトリルブロミド2.69gを加え、80度にて24時間攪拌した。不溶物を濾過し、濾液を減圧濃縮した。得られた残渣をヘキサン：酢酸エチル（10：１）を溶出溶媒とするシリカゲルカラムクロマトグラフィーにて精製した。得られた中間体3.1gをエタノール50ml及びテトラヒドロフラン10mlの混合溶媒に溶解し、これに酸化パラジウム硫酸バリウム錯体1gを加え、水素雰囲気下3日間室温で攪拌した。反応液をセライト濾過した後、濾液を減圧濃縮した。得られた残渣をヘキサン：酢酸エチル（2：１）を溶出溶媒とするシリカゲルカラムクロマトグラフィーにて精製し、エチル　３－アミノ－４－[２－（３－シアノフェニル）エチル]ベンゾアート2.35g得た。

参考例５

３－ヒドロキシ－２－ニトロベンゾイックアシッド　1.83g を N,N-ジメチルホルムアミド 50ml に溶解し、これに４－メトキシアニリン 1.23g、１－エチル－３－ジメチルアミノプロピルカルボジイミド 塩酸塩 2.50g、１－ヒドロキシベンゾトリアゾール 1.35g、及びトリエ

チルアミン 1.81ml を加え室温で 66 時間攪拌した。反応液を減圧濃縮し、水を加え、酢酸エチルで抽出した。この有機層を飽和食塩水で洗浄し、硫酸マグネシウムで乾燥し、減圧濃縮した。得られた残渣にクロロホルムを加え、生じた沈殿を濾取し、３－ヒドロキシー４’－メトキシー２－ニトロベンズアニリド 2.04g を得た。濾液をクロロホルム：メタノール(９８：2)を溶出溶媒とするシリカゲルカラムクロマトグラフィーにて精製し、得られた粗生成物にクロロホルムを加え生じた沈殿を濾取することにより、３－ヒドロキシー4’－メトキシ－２－ニトロベンズアニリド0.24gをさらに得た。

参考例６

３－ヒドロキシー4’－メトキシー２－ニトロベンズアニリド1.15gをメタノール50mlに懸濁し、10%パラジウム－カーボン粉末300mgを加え水素雰囲気下、室温で1時間攪拌した。反応液をセライト濾過し、メタノールで洗浄後、濾液を減圧下濃縮し、２－アミノ－３－ヒドロキシー４’－メトキシベンズアニリド966mgを得た。

参考例７

4-(4-メチル-1,4-ジアゼパン-1-イル)ベンゾニトリル 18.86 ｇを 12 N塩酸 185 ml に溶解し、80℃で 12 時間攪拌した後、減圧濃縮した。水を加え、室温で攪拌した後、生成した沈殿を濾過し水で洗った。得られた固体を減圧乾燥し 4-(4-メチル-1,4-ジアゼパン-1-イル)ベンゾイックアシッド　塩酸塩を 18.25 ｇ得た。

参考例８

4-(4-メチル-1,4-ジアゼパン-1-イル)ベンゾイックアシッド　塩酸塩１６．３ｇ、Ｎ，Ｎ－ジメチルホルムアミド０．８８ｇ、チオニルクロリド１４．３ｇ及び酢酸エチル１６０ｍＬの混合物を４０℃にて３時間攪拌後、減圧濃縮した。得られた残渣とアセトニトリル１３０ｍｌの混合物に、２－アミノ－３－ニトロフェノール８．３５ｇ、ピリジン９．５２ｇ及びアセトニトリル６０mLの溶液を氷冷下にて加えた。５℃以下で終夜攪拌した後、結晶を濾取し、２－アミノ－３－ニトロフェニル　４－（４－メチル－１，４－ジアゼパン-1-イル)ベンゾアート　塩酸塩２１．４ｇを得た。

参考例９

２－アミノ－３－ニトロフェニル　４－（４－メチル－１，４－ジアゼパン-1-イル)ベンゾアート　塩酸塩２．００ｇ、トリエチルアミン９９５ｍｇ及びアセトニトリル２０mLの混合物を７０℃にて６時間攪拌した。水酸化ナトリウム１９７ｍｇ及び水２mLの溶液を反

応液に加えた。水２０mLを加えた後、常圧にてアセトニトリルを加熱留去し、さらに水１０mLを加え、室温で１４時間攪拌した。析出した結晶を濾取し、２’－ヒドロキシ－４－（４－メチル－１，４－ジアゼパン-1-イル）－６’－ニトロベンズアニリド１．５７ｇを得た。

参考例１０

２’－ヒドロキシ－４－（４－メチル－１，４－ジアゼパン-1-イル）－６’－ニトロベンズアニリド２．１４ｇ、メタノール４３mL及び１０％パラジウム－炭素（ウェット率５４．２％）４６７mgの混合物を常圧水素雰囲気下、３０℃にて水素の吸収が止むまで攪拌した。触媒を濾去し、濾液を減圧濃縮した。残渣をシリカゲルクロマトグラフィー（クロロホルム：メタノール＝２０：１～１０：１）にて精製し、２’－アミノ－６’－ヒドロキシ－４－（４－メチル－１，４－ジアゼパン－１－イル）ベンズアニリド１．６１ｇを得た。

参考例１１

２－アミノ－３－ニトロフェノール３０８mgをピリジン１０ml に溶解し、４―メトキシベンゾイルクロリド３４１mgを０℃で加え、室温で１８時間攪拌した。反応液を減圧下濃縮し、得られた残査にクロロホルム２０ml を加え、再度減圧下濃縮した。この操作を更に３回繰り返しピリジンを除去した残査をクロロホルムを溶出溶媒とするシリカゲルカラムクロマトグラフィーで精製し２’－ヒドロキシ－４－メトキシ－６’－ニトロベンズアニリドを４２８mg得た。

参考例６と同様にして参考例１２の化合物を合成した。

参考例１３

３－ヒドロキシ－２－ニトロベンゾイックアシッド 10.5 g を N,N-ジメチルホルムアミド 60 ml に溶解し、ベンジルブロミド 15 ml、炭酸カリウム 19.0 g を０℃で加え、室温で１晩攪拌した。反応液をセライト濾過したのち、減圧下濃縮した。得られた残渣に水を加え、エーテルで抽出後、飽和食塩水で洗浄し、無水硫酸マグネシウムで乾燥した。溶媒を減圧下留去し、ベンジル　３－ベンジロキシ－２－ニトロベンゾアート 20.7 g を得た。

参考例１４

ベンジル　３－ベンジロキシ－２－ニトロベンゾアート 20.7 g にエタノール 100 ml および 1N 水酸化ナトリウム水溶液 120 ml を加え、室温で１晩、60℃で 3 時間、80℃で 5 時間攪拌した。エタノールを減圧下留去したのち、得られた水溶液をエーテルで洗った後、塩酸を

加えた。生じた沈殿を濾取した後、減圧下乾燥し、３－ベンジロキシ－２－ニトロベンゾイックアシッド 15.8 g を得た。

参考例１５

３－ベンジロキシ－２－ニトロベンゾイックアシッド 5.47 g にチオニルクロリド 20 ml および N,N-ジメチルホルムアミド数滴を加え、80℃で 30 分間攪拌した。反応液を減圧下濃縮し、得られた残渣に０℃でピリジン３５ｍｌおよび２－アミノ－５－クロロピリジン 2.55 g を加え、室温で１晩攪拌した。反応液を減圧下濃縮し、得られた残渣に飽和炭酸水素ナトリウム水溶液を加え、クロロホルムで抽出した。有機層を無水硫酸マグネシウムで乾燥し、溶媒を減圧下留去し、トルエン共沸を行い３－ベンジロキシ－*N*－（５－クロロ－２－ピリジル）－２－ニトロベンズアミド 7.44 g を得た。

参考例１６

３－ベンジロキシ－*N*－（５－クロロ－２－ピリジル）－２－ニトロベンズアミド 7.44 g にトリフルオロ酢酸 40 ml およびペンタメチルベンゼン 3.72 g を加え 40℃で１晩攪拌した。反応液を減圧下濃縮し、得られた残渣にアルカリ性にならない程度の飽和炭酸水素ナトリウム水溶液を加え、クロロホルムで抽出した。有機層を１Ｎ水酸化ナトリウム水溶液で抽出したのち、水層に塩酸を加え酸性とし、クロロホルムで抽出した。無水硫酸マグネシウムで乾燥後、溶媒を減圧下留去し得られた残渣にラネーニッケルのエタノール懸濁液 200 ml に加えた。水素雰囲気下 6 時間攪拌したのち、 N,N-ジメチルホルムアミドを加え、不溶物を濾去した。減圧下溶媒を留去し、得られた残査に水を加えた。生じた沈殿を濾取し、減圧下乾燥し、２－アミノ－*N*－（５－クロロ－２－ピリジル）－３－ヒドロキシベンズアミド 4.58 g を得た。

参考例１７

２－アミノ－*N*－（５－クロロ－２－ピリジル）－３－ヒドロキシベンズアミド 3.06 g とN-クロロスキシイミド1.80 gをN,N-ジメチルホルムアミド60 mlに溶解し５0℃で8時間、室温で4時間攪拌した後、不溶物を濾去した。減圧下溶媒を留去した後、得られた残査に１Ｎ水酸化ナトリウム水溶液を加え、酢酸エチルで抽出した。有機層を無水硫酸マグネシウムで乾燥後、溶媒を減圧下留去し、得られた残査をシリカゲルカラムクロマトグラフィーにより精製した。得られた粗精製物にエタノールを加え、生じた沈殿を濾取し、減圧下乾燥し、２－アミノ－５－クロロ－*N*－（５－クロロ－２－ピリジル）－３－ヒドロキシベンズアミド

767 mgを得た。母液を濃縮し、酢酸エチルーイソプロピルエーテルを加え、生じた沈殿を濾取した後、減圧下乾燥することにより、上記化合物をさらに942 mg得た。

参考例１７と同様にして参考例１８、１９の化合物を合成した。

参考例２０

エチル　２－アミノ－５－クロロ－３－ヒドロキシベンゾアート3.23 gを3規定塩酸水溶液160 mlに溶解し、８５℃で3時間、80℃で5日間攪拌した。反応液を室温まで冷却した後、不溶物を濾過し、濾液に１規定水酸化ナトリウム水溶液３２０ｍｌを加え、室温で１時間攪拌した。生じた沈殿を濾過し精製水で洗った後、減圧下乾燥し、２－アミノ－５－クロロ－３－ヒドロキシベンゾイックアシッド1.55 gを得た。

参考例２１

２－アミノ－５－クロロ－３－ヒドロキシベンゾイックアシッド1.12 gをN,N-ジメチルホルムアミド60 mlに溶解し、これに４－メトキシアニリン7.38 g、１－エチル－３－ジメチルアミノプロピルカルボジイミド 塩酸塩1.73 g、１－ヒドロキシベンゾトリアゾール1.21 g、及びトリエチルアミン1.26 mlを加え室温で13時間攪拌した。反応液を減圧濃縮し、得られた残査に酢酸エチルを加え、精製水と飽和食塩水で洗浄し、硫酸マグネシウムで乾燥した後、減圧下濃縮した。得られた残渣にクロロホルムを加え、30分間攪拌した後、生じた沈殿を濾取し、クロロホルムで洗浄した後、減圧下乾燥し２－アミノ－５－クロロ－３－ヒドロキシ－４’－メトキシ－２－ベンズアニリド0.96 gを得た。

参考例２２

4-(4-メチル-１，4-ジアゼパン-１-イル)ベンゾイックアシッド　塩酸塩５．０９ｇにチオニルクロリド４０ｍｌを加え、６０℃で３０分間攪拌した。反応液を減圧下濃縮乾固した。得られた残渣に、エチル　３－アミノ－４－［（３－シアノフェニルアミノ）メチル］ベンゾアート５．６５ｇをピリジン５０ｍｌに溶解した溶液を加え、室温で５時間攪拌した。反応液を減圧下濃縮した後、得られた残渣に酢酸エチルとクロロホルムをを加え、飽和炭酸水素ナトリウム水溶液と、飽和食塩水で洗い、無水硫酸マグネシウムで乾燥後、減圧下濃縮した。得られた残渣をヘキサン：酢酸エチル（９５：５～９０：１０）を溶出溶媒とするシリカゲルカラムクロマトグラフィーで精製し、エチル　４－［（３－シアノフェニルアミノ）メチル］－３－［4-(4-メチル-１，4-ジアゼパン-１-イル)ベンゾイルアミノ］ベンゾアートを６．４２ｇ得た。

参考例２２と同様にして参考例２３の化合物を合成した。

実施例１

エチル　４－［（３－シアノフェニルアミノ）メチル］－３－［4-(4-メチル-１，４-ジアゼパン-1-イル)ベンゾイルアミノ］ベンゾアート４．０９ｇをエタノール８０ｍｌに溶解し、－２０℃以下で塩酸ガスを２０分間通導した後、３℃まで昇温し、２４時間攪拌した。反応液を減圧下濃縮乾固し、得られた残渣をエタノール８０ｍｌに溶解し、酢酸アンモニア６．１６ｇを加え室温で３．５日間攪拌した。反応液を減圧下濃縮し、得られた残渣を０．００２規定塩酸水溶液：エタノール（１００：０～８０：２０）を溶出溶媒とするＯＤＳカラムクロマトグラフィーで精製し、エチル　４－［（３－カルバミミドイルフェニルアミノ）メチル］－３－［4-(4-メチル-１，４-ジアゼパン-１-イル)ベンゾイルアミノ］ベンゾアート　塩酸塩を３．８４ｇ得た。得られた化合物の内、１．７０ｇをエタノール２０ｍｌに溶解し、１規定水酸化ナトリウム水溶液３０ｍｌを加え室温で１時間攪拌した。反応液を１規定塩酸水溶液で中和した後、減圧下濃縮た。得られた残渣を０．００２規定塩酸水溶液：アセトニトリル（１００：０～９２：８）を溶出溶媒とするＯＤＳカラムクロマトグラフィーで精製した後、凍結乾燥し、４－［（３－カルバミミドイルフェニルアミノ）メチル］－３－［4-(4-メチル-１，４-ジアゼパン-１-イル)ベンゾイルアミノ］ベンゾイックアシッド　塩酸塩を１．４８ｇ得た。

実施例２

エチル　４－［（３－シアノフェニルアミノ）メチル］－３－［4-(4-メチル-１，４-ジアゼパン-１-イル)ベンゾイルアミノ］ベンゾアート１．４２ｇをエタノール３０ｍｌに溶解し、ヒドロキシルアミン塩酸塩２９１ｍｇ及び、トリエチルアミン０．７８ｍｌを加え６０℃で２４時間攪拌した。反応液を減圧下濃縮し、得られた残渣をクロロホルム：メタノール：アンモニア水溶液（１００：０：０～９２：８：０．８）を溶出溶媒とするシリカゲルカラムクロマトグラフィーで精製し、エチル　４－（｛［３－（Ｎ－ヒドロキシカルバミミドイル）フェニル］アミノ｝メチル）－３－［4-(4-メチル-１，４-ジアゼパン-１-イル)ベンゾイルアミノ］ベンゾアートの粗精製物を得た。さらに０．００２規定塩酸水溶液：メタノール（１００：０～８８：１２）を溶出溶媒とするＯＤＳカラムクロマトグラフィーで精製した後、凍結乾燥し、エチル　４－（｛［３－（Ｎ－ヒドロキシカルバミミド

イル）フェニル］アミノ｝メチル）－３－［4-(4-メチル-1，4-ジアゼパン-1-イル)ベンゾイルアミノ］ベンゾアート　塩酸塩を１．０３ｇを得た。

実施例１と同様にして実施例３、５、７、５４の化合物を合成した

実施例２と同様にして実施例４、６、８、５３の化合物を合成した

実施例９

４－（４－メチル－１，４－ジアゼパン－１－イル）ベンゾイックアシッド　塩酸塩８１２ｍｇをチオニルクロリド８ｍｌに溶解し、６０℃で３０分攪拌した。反応液を減圧下濃縮乾固した。得られた残渣に、２－アミノ－4'－メトキシ－３－ヒドロキシベンズアニリド７７４ｍｇをピリジン１５ｍｌに溶解した溶液を０℃で加え、室温で２時間攪拌した。反応液を減圧下濃縮した後、得られた残渣にトルエンを加え再度減圧下濃縮した。得られた残渣に飽和炭酸水素ナトリウム水溶液と酢酸エチルを加え、得られた沈殿を濾取した。母液の酢酸エチル層を無水硫酸ナトリウムで乾燥した後、減圧下濃縮した。得られた残渣と濾取した沈殿を混合しクロロホルム：メタノール（９８：２）を溶出溶媒とするシリカゲルカラムクロマトグラフィーで精製し、３－ヒドロキシ－4'－メトキシ－２－｛［４－（４－メチル－１，４－ジアゼパン－１－イル）ベンゾイル］アミノ｝ベンズアニリドを８７３ｍｇ得た。得られた化合物をエタノール１０ｍｌに懸濁し、４規定塩酸酢酸エチル溶液０．７ｍｌを加え攪拌した後、生じた沈殿を濾過し、エタノールで洗浄し、減圧下乾燥することにより３－ヒドロキシ－4'－メトキシ－２－｛［４－（４－メチル－１，４－ジアゼパン－１－イル）ベンゾイル］アミノ｝ベンズアニリド　塩酸塩を８９６ｍｇ得た。

実施例９と同様にして実施例１０～１６、４２、５１、５２の化合物を合成した。

実施例１７

２’－アミノ－６’－ヒドロキシ－４－（４－メチル－１，４－ジアゼパン－１－イル）ベンズアニリド２．０３ｇをピリジン６０ｍｌに溶解し、４―メトキシベンゾイルクロリド１．１２ｇを0℃で加え、室温で３日間攪拌した。反応液を減圧下濃縮し、得られた残査にクロロホルム１５０ｍｌを加え、５％炭酸水素ナトリウム水溶液１５０ｍｌでアルカリ性とし、クロロホルムで抽出した。得られた有機層を無水硫酸ナトリウムで乾燥した後、減圧下濃縮し、トルエンを加え、再度減圧下濃縮した。得られた残査をクロロホルム：メタノール：飽和アンモニア水（１００：１０：１）を溶出溶媒とするシリカゲルカラムクロマトグラフィーで精製した。エタノールより再結晶し、３－ヒドロキシ－N^1―（４－メトキシベ

ンゾイル）－N^2－［4－（4－メチル－1，4－ジアゼパン－1－イル）ベンゾイル］－1，2－フェニレンジアミン1．74gを得た。3－ヒドロキシ－N^1－（4－メトキシベンゾイル）－N^2－［4－（4－メチル－1，4－ジアゼパン－1－イル）ベンゾイル］－1，2－フェニレンジアミン1．10gとマレイン酸269mgを50％エタノール水溶液11mlに加熱溶解し、水11mlを加え冷却し生じた結晶を濾取、乾燥し、3－ヒドロキシ－N^1－（4－メトキシベンゾイル）－N^2－［4－（4－メチル－1，4－ジアゼパン－1－イル）ベンゾイル］－1，2－フェニレンジアミン　マレイン酸塩を1．18g得た。

実施例17と同様にして実施例18～35の化合物を合成した。

実施例36

3－ヒドロキシ－N^1－（4－メトキシベンゾイル）－N^2－［4－（4－メチル－1，4－ジアゼパン－1－イル）ベンゾイル］－1，2－フェニレンジアミン500mgをメタノール11mlに溶解し、室温にて臭化ベンジル215mgを加え5時間攪拌した。室温にて臭化ベンジル215mgを加え16時間攪拌した後、析出物を濾取した。得られた析出物をN，N－ジメチルホルムアミド11mlに懸濁させ、室温にてブロモ酢酸エチル210mgと炭酸カリウム174mgを加え、100℃にて30分間攪拌した。不溶物を濾過し、減圧下濃縮した。得られた残渣を酢酸16mlに溶解し、10％パラジウム－カーボン粉末100mgを加え、3気圧の水素雰囲気下、室温にて3時間攪拌した。反応液をセライト濾過し、メタノールで洗浄後、濾液を減圧下濃縮した。得られた残査にクロロホルム50mlを加え、5％炭酸水素ナトリウム水溶液50mlでアルカリ性とし、クロロホルムで抽出した。得られた有機層を無水硫酸ナトリウムで乾燥した後、減圧下濃縮した。得られた残渣をクロロホルム：メタノール：飽和アンモニア水（100：10：1）を溶出溶媒とするシリカゲルカラムクロマトグラフィーで精製し、エチル　（3－［（4－メトキシベンゾイル）アミノ］－2－｛［4－（4－メチル－1，4－ジアゼパン－1－イル）ベンゾイル］アミノ｝フェノキシ）アセタートの粗精製物を580mg得た。その粗精製物を0．001規定塩酸：メタノール（10：4）を溶出溶媒とするODSカラムクロマトグラフィーで精製し、エチル　（3－［（4－メトキシベンゾイル）アミノ］－2－｛［4－（4－メチル－1，4－ジアゼパン－1－イル）ベンゾイル］アミノ｝フェノキシ）アセタート 塩酸塩350mgを得た。

実施例37

エチル （3－［（4－メトキシベンゾイル）アミノ］－2－｛［4－（4－メチル－1，4－ジアゼパン－1－イル）ベンゾイル］アミノ｝フェノキシ）アセタート塩酸塩350mgをメタノール6ml に溶解し、室温にて1規定水酸化ナトリウム水溶液1．8ml を加え2時間攪拌した。1規定塩酸1．8ml を加え、減圧下濃縮した。得られた残渣を0．001規定塩酸：アセトニトリル（1：1）を溶出溶媒とするODSカラムクロマトグラフィーで精製し、（3－［（4－メトキシベンゾイル）アミノ］－2－｛［4－（4－メチル－1，4－ジアゼパン－1－イル）ベンゾイル］アミノ｝フェノキシ）アセティック アシッド塩酸塩254mgを得た。

実施例37と同様にして実施例38の化合物を合成した。

実施例39

エチル （3－［（4－メトキシベンゾイル）アミノ］－2－｛［4－（4－メチル－1，4－ジアゼパン－1－イル）ベンゾイル］アミノ｝フェノキシ）アセタートの粗精製物370mgをテトラヒドロフラン7ml に溶解し、室温にてテトラヒドロホウ酸ナトリウム108mgを加えた。そこへメタノール930mgをテトラヒドロフラン7ml に溶解した溶液を、60℃にて25分間かけて滴加した。60℃にて2時間攪拌した。水1ml を室温にて加え、減圧下濃縮した。得られた残渣に対し上述の操作を再度施した後、得られた残渣をクロロホルム：メタノール：飽和アンモニア水（100：10：1）を溶出溶媒とするシリカゲルカラムクロマトグラフィーで精製した。得られた化合物をエタノール3ml に懸濁し、1規定塩酸0．4ml を加え減圧下濃縮した。得られた残渣にアセトン3ml と蒸留水3ml を加え、生じた沈殿を濾過し、3－（2－ヒドロキエトキシ）－N^1－（4－メトキシベンゾイル）－N^2－［4－（4－メチル－1，4－ジアゼパン－1－イル）ベンゾイル］－1，2－フェニレンジアミン 塩酸塩107mgを得た。

実施例40

3－ヒドロキシ－N^1－（4－メトキシベンゾイル）－N^2－［4－（4－メチル－1，4－ジアゼパン－1－イル）ベンゾイル］－1，2－フェニレンジアミン730mgをテトラヒドロフラン20ml に溶解し、メタノール0．13ml、トリフェニルフォスフィン498mg、ジエチル アゾジカルボキシラート0．23ml を加え、室温で16．5時間攪拌した。反応液を減圧濃縮した後、得られた残渣をクロロホルムに溶解し、0．5規定水酸化ナトリウム水溶液と飽和食塩水で洗浄し、無水硫酸ナトリウムで乾燥した後、減圧濃縮した。

得られた残査をクロロホルム：メタノール（９５：５～９３：７）を溶出溶媒とするシリカゲルカラムクロマトグラフィーで精製した。得られた粗精製物をエタノール１０ｍｌに溶解し４規定塩酸酢酸エチル溶液を０．４ｍｌ加えた後、減圧濃縮した。得られた残渣を０．０２Ｎ塩酸水溶液：アセトニトリル（９７：３～８５：１５）を溶出溶媒とするＯＤＳカラムクロマトグラフィーで精製した後、凍結乾燥し３－メトキシ－N^1－（４－メトキシベンゾイル）－N^2－［４－（４－メチル－１，４－ジアゼパン－１－イル）ベンゾイル］－１，２－フェニレンジアミン　塩酸塩３３５ｍｇを得た

実施例４１

３－ヒドロキシ－N^1－（４－メトキシベンゾイル）－N^2－［４－（４－メチル－１，４－ジアゼパン－１－イル）ベンゾイル］－１，２－フェニレンジアミン４７４ｍｇをＮ，Ｎ－ジメチルホルムアミド１５ｍｌに溶解し、トリメチルアミン－サルファートリオキサイド錯体１．３９ｇを加え６０度で７９時間攪拌した。さらにトリメチルアミン－サルファートリオキサイド　錯体０．４２ｇを加え６０度で３８時間攪拌し、さらにトリメチルアミン－サルファートリオキサイド　錯体０．４２ｇを加え６０度で２３時間攪拌した後、減圧濃縮した。得られた残渣に水を加え、１時間攪拌した後、生じた沈殿を濾取し、水で洗った。得られた粗精製物をエタノールに懸濁、攪拌した後濾過し、エタノールと水で洗った後、減圧乾燥し３－［（４－メトキシベンゾイル）アミノ］－２－｛［４－（４－メチル－１，４－ジアゼパン－１－イル）ベンゾイル］アミノ｝フェニル　ハイドロゲン　サルフェート４８３ｍｇを得た。

実施例４３

N^2－［４－（４－ベンジル－１，４－ジアゼパン－１－イル）ベンゾイル］－３－ヒドロキシ－N^1－（４－メトキシベンゾイル）－１，２－フェニレンジアミン１１．５３ｇを酢酸２５０ｍｌに溶解し１０％パラジウム－カーボン粉末２．５ｇを加え３気圧水素雰囲気下、室温で４４時間攪拌した。反応液をセライト濾過し、酢酸で洗浄後、濾液を減圧濃縮した。トルエンを加え再び減圧濃縮し、１１．１１ｇの残渣を得た。その残渣の内、２．００ｇをクロロホルム、炭酸水素ナトリウム水溶液、メタノールの混合溶媒に溶解し、１２時間攪拌した。有機層を分離後、飽和食塩水で洗い、無水硫酸ナトリウムで乾燥し、減圧濃縮した。得られた残渣をエタノールに懸濁し３時間攪拌した後、沈殿物を濾過し、エタノールで洗った。得られた固体をエタノールから再結晶し、N^2－［４－（１，４－ジアゼパン－１

－イル）ベンゾイル］－３－ヒドロキシ－N^1－（４－メトキシベンゾイル）－１，２－フェニレンジアミンを得た。さらに０．５NHC１から結晶化させ、N^2－［４－（１，４－ジアゼパン－１－イル）ベンゾイル］－３－ヒドロキシ－N^1－（４－メトキシベンゾイル）－１，２－フェニレンジアミン　塩酸塩８７８mgを得た。

実施例４４

３－ヒドロキシ－N^1－（４－メトキシベンゾイル）－N^2－［４－（１，４－ジアゼパン－１－イル）ベンゾイル］－１，２－フェニレンジアミン８５７mgをジクロロエタン２０ｍｌに懸濁し、室温にて酢酸１．２ｇとシクロプロパンカルバルデヒド２６１mgとトリアセトキシボロヒドリド７８９mgを加えた。２時間攪拌した後、室温にてシクロプロパンカルバルデヒド２６１mgとトリアセトキシボロヒドリド７８９mgを加え、さらに２時間攪拌した。反応液を減圧下濃縮した後、得られた残査にクロロホルム５０ｍｌを加え、５％炭酸水素ナトリウム水溶液５０ｍｌでアルカリ性とし、クロロホルムで抽出した。得られた有機層を無水硫酸ナトリウムで乾燥した後、減圧下濃縮した。得られた残渣をクロロホルム：メタノール：飽和アンモニア水（１００：１０：１）を溶出溶媒とするシリカゲルカラムクロマトグラフィーで精製した。得られた化合物をエタノール１３ｍｌに懸濁し、１規定塩酸１．９ｍｌを加え、生じた沈殿を濾過し、３－ヒドロキシ－ N^1－（４－メトキシベンゾイル）－N^2－［４－（４－シクロプロピルメチル－１，４－ジアゼパン－１－イル）ベンゾイル］－１，２－フェニレンジアミン 塩酸塩６５６mgを得た。

実施例４５

N^2－［４－（１，４－ジアゼパン－１－イル）ベンゾイル］－３－ヒドロキシ－N^1－（４－メトキシベンゾイル）－１，２－フェニレンジアミン１．３ｇをエタノール２０ｍｌに溶解し、エチル　アセトイミダート　塩酸塩１．０４ｇとトリエチルアミン１．５ｍｌを加え１７時間攪拌した。エタノール１５０ｍｌ、エチル　アセトイミダート　塩酸塩１．０４ｇ、トリエチルアミン１．５ｍｌをさらに加え５０℃で６８時間攪拌した。反応液を減圧濃縮し、得られた残渣を０．００２N塩酸水溶液：アセトニトリル（９５：５～７０：３０）を溶出溶媒とするＯＤＳカラムクロマトグラフィーで精製した後、凍結乾燥し３－ヒドロキシ－N^2－｛４－［４－（１－イミノエチル）－１，４－ジアゼパン－１－イル］ベンゾイル｝－N^1－（４－メトキシベンゾイル）－１，２－フェニレンジアミン　塩酸塩５１５mgを得た

実施例４４と同様にして実施例４６～４８の化合物を合成した。

実施例４９

４－（４－メチル－１，４－ジアゼパン－１－イル）ベンゾイックアシッド　塩酸塩 755 mg をチオニルクリド 2.2 ml に溶解し、60℃で 30 分攪拌した。反応液を減圧下濃縮乾固した。得られた残渣に、２－アミノ－５－クロロ－*N*－（５－クロロ－２－ピリジル）－３－ヒドロキシベンズアミド 891 mg をピリジン 10 ml に溶解した溶液を加え、室温で 13 時間攪拌した。反応液を減圧下濃縮した後、得られた残査に酢酸 20 ml を加え室温で１７時間攪拌した。反応液を減圧下濃縮した後、得られた残査に飽和炭酸水素ナトリウム水溶液を加えクロロホルムで抽出し、無水硫酸ナトリウムで乾燥した後、減圧下濃縮した。得られた残渣をクロロホルム：メタノール：アンモニア水（97：3:0.3～95:5:0.5）を溶出溶媒とするシリカゲルカラムクロマトグラフィーで精製し、５－クロロ－*N*－（５－クロロ－２－ピリジル）－３－ヒドロキシ－２－｛［４－（４－メチル－１，４－ジアゼパン－１－イル）ベンゾイル］アミノ｝ベンズアミドの粗精製物を得た。これをさらにアセトニトリル：０．００２規定塩酸水溶液（2:8～3:7）を溶出溶媒とするＯＤＳカラムクロマトグラフィーで精製し、希塩酸水溶液に懸濁後凍結乾燥し５－クロロ－*N*－（５－クロロ－２－ピリジル）－３－ヒドロキシ－２－｛［４－（４－メチル－１，４－ジアゼパン－１－イル）ベンゾイル］アミノ｝ベンズアミド　塩酸塩 492 mg を得た。

実施例４９と同様にして実施例５０の化合物を合成した。

前記参考例化合物及び実施例化合物の構造式と物理化学的性状を、別表２及び３に示す。表４～６に示される化合物は、前記実施例若しくは製造法に記載の方法とほぼ同様にして、又はそれらに当業者に自明の若干の変法を適用して容易に製造することができる。なお、表中の記号は以下の意味を有する。

Ｒｆ：参考例番号、Ｅｘ：実施例番号、structure：構造式、salt：塩、free：遊離体、DATA：物性データ、ＮＭＲ：核磁気共鳴スペクトル（ＴＭＳ内部標準）、FAB-MS：質量分析値、Ｍｅ：メチル、Ｅｔ：エチル

表2

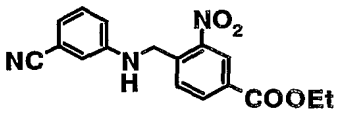
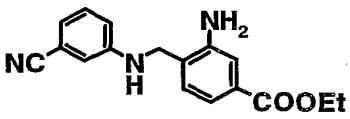
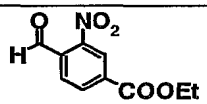
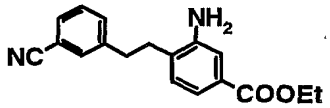
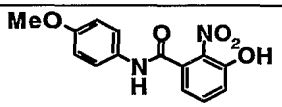
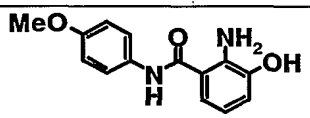
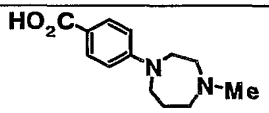
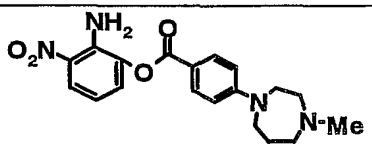
Rf	structure(salt)	DATA
1	 (free)	NMR($CDCl_3$): δ:1.42(3H, t, J = 7.2 Hz), 4.43(2H, q, J = 7.2Hz), 4.63(1H, t, J = 5.7 Hz), 4.81(2H, d, J = 6.0 Hz), 6.72 - 6.78(2H, m), 7.01(1H, dt, J = 1.3 Hz, 7.7 Hz), 7.19 - 7.27(1H, m), 7.69(1H, d, J = 8.1 Hz), 8.24(1H, dd, J = 1.7 Hz, 8.0 Hz), 8.73(1H, d, J = 1.7 Hz)
2	 (free)	NMR($CDCl_3$): δ:1.39(3H, t, J = 7.1 Hz), 3.96 - 4.16(3H, m), 4.25(2H, d, J = 4.2 Hz), 4.36(2H, q, J = 7.1Hz), 6.85 - 6.93(2H, m), 7.05(1H, dt, J = 1.2 Hz, 7.9 Hz), 7.22(1H, d, J = 7.7 Hz), 7.27(1H, t, J = 8.0 Hz), 7.41(1H, d, J = 1.3 Hz), 7.43(1H, dd, J = 1.7 Hz, 7.7 Hz)
3	 (free)	NMR($CDCl_3$): δ: 1.46(3H, t, J=7.2Hz), 4.48(2H, q, J=7.2Hz), 8.00(1H, d, J=8.0Hz), 8.42(1H, d, J=8.0Hz), 8.75(1H, s), 10.46(1H, s)
4	 (free)	NMR($CDCl_3$): δ: 1.38(3H, t, J=7.1Hz), 2.82(2H, t, J=8.4Hz), 2.96(2H, t, J=8.4Hz), 4.34(2H, q, J=7.1Hz), 6.97(1H, d, J=8.4Hz), 7.33-7.41(4H, m), 7.44-7.52(2H, m)
5	 (free)	NMR(DMSO-d_6): δ: 3.74(3H, s), 6.92(2H, d, J = 8.8 Hz), 7.19 - 7.30(2H, m), 7.50(1H, t, J = 8.6 Hz), 7.58(2H, d, J = 9.3 Hz), 10.46(1H, s), 11.25(1H, brs),
6	 (free)	NMR(DMSO-d_6): δ: 3.74(3H, s), 5.79(2H, s), 6.46(1H, t, J = 7.8 Hz), 6.82(1H, d, J = 7.8 Hz), 6.90(2H, d, J = 8.8 Hz), 7.15(1H, d, J = 7.8 Hz), 7.61(2H, d, J = 8.8 Hz), 9.56(1H, s), 9.81(1H, s),
7	 HCl	NMR(DMSO-d_6): δ:2.06 - 2.24(1H, m), 2.30 - 2.45(1H, m), 2.77(3H, s), 3.00 - 3.24(2H, m), 3.24 - 3.55(4H, m), 3.70 - 4.00(2H, m), 6.81(2H, d, J = 9.1 Hz), 7.78(2H, d, J = 9.1 Hz), 11.06(1H, s), 12.20(1H, s)
8	 HCl	NMR(DMSO-d_6) δ:2.15 - 2.22(1H, m), 2.34-2.45(1H, m), 2.79(3H, d, J = 5.0Hz), 3.05 - 3.22(2H, m), 3.40 - 3.61(4H, m), 3.79 - 3.88(1H, m), 3.95 - 4.03(1H, m), 6.69 - 6.75(1H, m), 6.93(2H, d, J = 9.0 Hz), 7.05(2H, br), 8.00(2H, d, J = 9.0 Hz), 11.12(1H, br)

表２（続き）

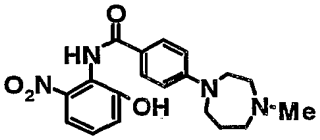
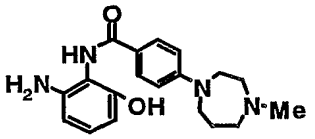
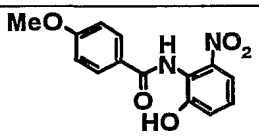
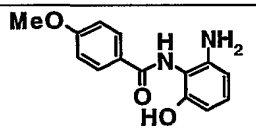
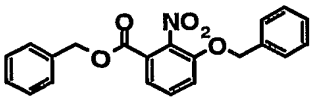
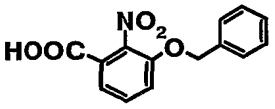
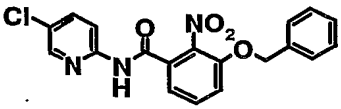
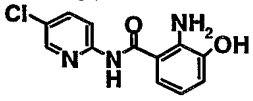
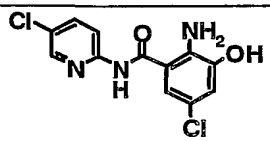
9	 (free)	NMR(DMSO-d_6) δ:1.86-1.95(2H, m), 2.29(3H, s), 2.45 - 2.52(2H, m), 2.65(2H, t, J = 4.4Hz), 3.51(2H, t, J = 6.0 Hz), 3.60(2H, t, J = 4.4 Hz), 6.76(2H, d, J = 9.2 Hz), 7.21-7.28(2H, m), 7.35(1H, dd, J = 6.8Hz, 2.4 Hz), 7.84(2H, d, J = 9.2Hz), 9.53(1H, br)
10	 (free)	NMR(DMSO-d_6): 1.85-1.94(2H, m), 2.26(3H, s), 2.43(2H, t, J=5.6Hz), 2.61(2H, t, J=4.8Hz), 3.51(2H, t, J=6.0Hz), 3.58(2H, t, J=4.8Hz), 4.68(2H, s), 6.16(1H, dd, J=7.6Hz, 1.2Hz), 6.24(1H, dd, J=8.0Hz, 1.2Hz), 6.70-6.81(3H, m), 7.86(1H, d, J=8.8Hz), 8.93(1H, br), 8.94(1H, s)
11	 (free)	NMR(DMSO-d_6): δ:3.88(3H, s), 6.70(1H, dd, J = 7.7 Hz, 8.7 Hz), 7.14(2H, d, J = 8.9 Hz), 7.17 - 7.21(2H, m), 7.43(1H, dd, J = 1.4 Hz, 7.7 Hz), 7.97(1H, dd, J = 1.4 Hz, 8.7 Hz), 8.13(2H, d, J = 8.9 Hz)
12	 (free)	NMR(DMSO-d_6): δ:3.83 - 3.86(2H, m), 3.84(3H, s), 6.68 - 6.72 (1H,m), 6.72 - 6.78(1H, m), 7.06(2H, d, J = 8.7 Hz), 7.06 - 7.12(2H, m), 8.05(2H, d, J = 8.7 Hz), 9.63 - 9.67(1H, br)
13	 (free)	NMR(DMSO-d_6): δ:5.33(4H, s), 7.31 - 7.45 (10H,m), 7.61(1H, dd, J = 1.4 Hz, 7.5 Hz), 7.68(1H, t, J = 7.9 Hz), 7.74(1H, dd, J = 1.5 Hz, 8.2 Hz)
14	 (free)	NMR(DMSO-d_6): δ:5.32(2H, s), 7.31 - 7.44 (5H,m), 7.56(1H, dd, J = 1.7 Hz, 7.3 Hz), 7.64(1H, t, J = 7.9 Hz), 7.68(1H, dd, J = 1.7 Hz, 8.3 Hz)
15	 (free)	NMR($CDCl_3$): δ:5.23(2H, s), 7.22 - 7.26 (2H,m), 7.31 - 7.39 (5H,m), 7.46(1H, t, J = 8.3 Hz), 7.69(1H, dd, J = 2.7 Hz, 9.1 Hz), 8.03(1H, d, J = 2.9 Hz), 8.26(1H, d, J = 8.8 Hz), 9.01(1H, brs)
16	 (free)	NMR(DMSO-d_6): δ:5.93(2H, s), 6.44(1H, t, J = 7.9Hz), 6.82(1H, d, J = 7.7 Hz), 7.27(1H, d, J = 7.3 Hz), 7.93(1H, dd, J = 2.6 Hz, 9.0 Hz), 8.14(1H, d, J = 8.8 Hz), 8.41(1H, d, J = 2.4 Hz), 9.60(1H, s), 10.46(1H, s)
17	 (free)	NMR(DMSO-d_6): δ:6.04(2H, brs), 6.80(1H, d, J = 2.4 Hz), 7.36(1H, d, J = 2.0 Hz), 7.93(1H, dd, J = 2.5 Hz, 8.8 Hz), 8.11(1H, d, J = 9.3 Hz), 8.42(1H, d, J = 2.5 Hz), 10.16(1H, brs), 10.67(1H, s)

表2（続き）

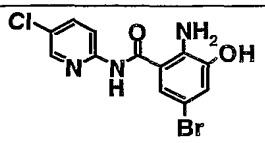
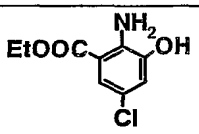
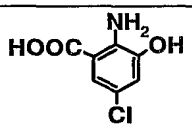
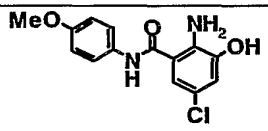
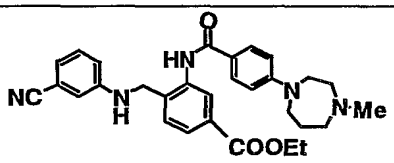
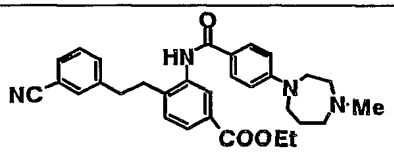
18	 (free)	NMR(DMSO-d_6)： δ：6.06(2H, brs), 6.90(1H, d, J = 2.2 Hz), 7.47(1H, d, J = 2.2 Hz), 7.93(1H, dd, J = 2.8 Hz, 9.0 Hz), 8.10(1H, d, J = 9.0 Hz), 8.42(1H, d, J = 2.2 Hz), 10.15(1H, brs), 10.69(1H, s)
19	 (free)	NMR($CDCl_3$)： δ：1.38(3H, t, J = 7.3 Hz), 4.33(2H, q, J = 7.3 Hz), 5.00 - 6.30(3H br), 6.81(1H, d, J = 2.0 Hz), 7.48(1H, d, J = 2.4 Hz)
20	 (free)	NMR(DMSO-d_6)： δ：3.37(1.5H, brs), 6.78(1H, d, J = 2.4 Hz), 7.17(1H, d, J = 2.5 Hz), 8.34(1.5H, brs), 10.19(1H, s)
21	 (free)	NMR(DMSO-d_6)： δ：3.74(3H, s), 5.93(2H, brs), 6.78(1H, d, J = 1.9 Hz), 6.91(2H, d, J = 9.3 Hz), 7.23(1H, d, J = 2.5 Hz), 7.59(2H, d, J = 9.3 Hz), 9.90(1H, s), 10.09(1H, brs)
22	 (free)	NMR($CDCl_3$)： δ：1.39(3H, t, J = 7.4 Hz), 1.97 - 2.06(2H, m), 2.38(3H, s), 2.53 - 2.59(2H, m), 2.68 - 2.73(2H, m), 3.51(2H, t, J = 6.4 Hz), 3.57 - 3.63(2H, m), 4.34 - 4.42(5H, m), 6.58(2H, d, J = 8.8 Hz), 6.96 - 7.01(2H, m), 7.12(1H, d, J = 7.8 Hz), 7.31(1H, t, J = 7.8 Hz), 7.40(1H, d, J = 8.3 Hz), 7.65 (2H, d, J = 8.7 Hz), 7.81(1H, dd, J = 1.5 Hz, 7.8 Hz), 8.67(1H, d, J = 2.0 Hz), 8.85(1H, s), FAB-MS(m/z)：512 $(M+H)^+$
23	 (free)	NMR($CDCl_3$)： δ：1.37(3H, t, J=7.1Hz), 2.43-2.54(2H, br), 2.76(3H, s), 2.93-3.01(4H, m), 3.14-3.22(2H, br), 3.23-3.29(2H, br), 3.59(2H, t, J=6.4Hz), 3.89-3.95(2H, m), 4.33(2H, q, J=7.1Hz), 6.72(2H, d, J=8.9Hz), 7.20(1H, d, J=7.3Hz), 7.27-7.35(3H, m), 7.41(1H, d, J=7.3Hz), 7.68-7.73(1H, m), 7.75(2H, d, J=8.3Hz), 7.85(1H, dd, J=1.8Hz, 8.3Hz), 8.23(1H, s) FAB-MS(m/z)：511 $(M+H)^+$

表3

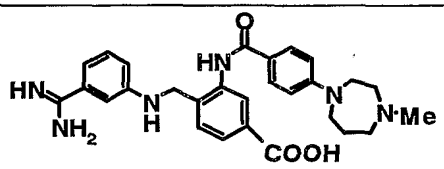
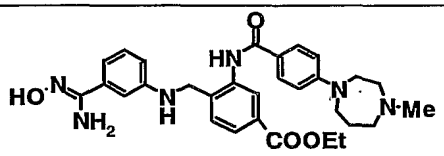
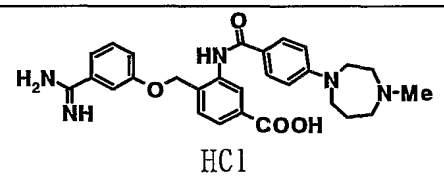
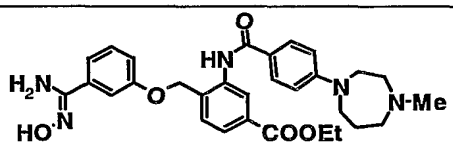
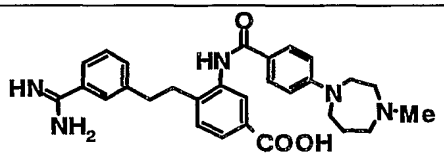
Ex	structure(salt)	DATA
1	 HCl	NMR(DMSO-d_6): δ:2.16-2.26(2H, br), 2.67(3H, s), 2.95 - 3.49(5H, br), 3.54(2H, t, J = 6.3 Hz), 3.73-3.86(2H, br), 4.44(2H, d, J = 5.3 Hz), 6.79 - 6.87(4H, m), 6.94(1H, d, J = 7.3 Hz), 6.98 (1H, s), 7.26(1H, t, J = 8.3 Hz), 7.44(1H, d, J = 7.8 Hz), 7.75(1H, dd, J = 2.0 Hz, 7.8 Hz), 7.94 (2H, d, J = 9.2 Hz), 7.98(1H, d, J = 1.9 Hz), 9.07(2H, s), 9.22(2H, s), 9.98(2H, s) FAB-MS(m/z): 501 $(M+H)^+$
2	 HCl	NMR(DMSO-d_6): δ:1.31(3H, t, J = 7.3 Hz), 2.79(3H, d, J = 4.4 Hz), 4.31(2H, q, J = 7.3 Hz), 4.43(2H, s), 6.76 - 6.91(6H, m), 7.25(1H, t, J = 8.4 Hz), 7.46(1H, d, J = 8.3 Hz), 7.77(1H, dd, J = 8.3, 1.4 Hz), 7.96(2H, d, J = 8.8 Hz), 8.01(1H, d, J = 1.4 Hz), FAB-MS(m/z): 545 $(M+H)^+$
3	 HCl	NMR(DMSO-d_6): δ: 2.02 - 2.09(2H, m), 2.76 - 2.84(2H, m), 2.87 - 2.98(2H, m), 3.32(3H, br s), 3.51 - 3.55(2H, m), 3.68 - 3.73(2H, m), 5.31(2H, s), 6.81(2H, d, J = 8.8 Hz), 7.31(1H, dd, J = 2.4 Hz , 8.4 Hz), 7.40(1H, d, J = 8.0 Hz), 7.46 - 7.49(1H, m), 7.50 - 7.54(1H, m), 7.62(1H, d, J = 8.4 Hz), 7.82(1H, dd, J = 2.0 Hz , 8.0 Hz), 7.89 (2H, d, J = 8.8 Hz), 8.03 (1H, d, J = 1.6 Hz), 9.33(4H, br s), 9.90(1H, s) FAB-MS(m/z): 502 $(M+H)^+$
4	 HCl	NMR(DMSO-d_6): δ: 1.33(3H, t, J = 7.4 Hz), 2.79(3H, s), 4.32(2H, q, J = 7.3 Hz), 5.26(2H, s), 6.86(2H, d, J = 8.8 Hz), 7.03 - 7.08(1H, m), 7.26 - 7.37(3H, m), 7.67(1H, d, J = 8.4 Hz), 7.84(1H, dd, J = 1.6 Hz , 8.4 Hz), 7.91 (2H, d, J = 8.8 Hz), 8.10 (1H, d, J = 1.6 Hz), FAB-MS(m/z): 546 $(M+H)^+$
5	 HCl	NMR(DMSO-d_6): δ: 2.12-2.24(1H, m), 2.38-2.49(1H, m), 2.79(3H, d, J=4.9Hz), 3.92-3.99(2H, m), 3.01-3.20(4H, m), 3.39-3.58(4H, m), 3.76-3.85(1H, m), 3.90-4.03(1H, m), 6.86(2H, d, J=9.3Hz), 7.41(1H, d, J=8.3Hz), 7.43-7.49(2H, m), 7.61-7.67(1H, m), 7.75(2H, dd, J=1.5Hz, 9.3Hz), 7.88(1H, d, J=1.5Hz), 7.98(2H, d, J=9.3Hz), 9.35(2H, s), 9.45(2H, s), 9.91(1H, s), 11.37(1H, s) FAB-MS(m/z): 500 $(M+H)^+$

表３（続き）

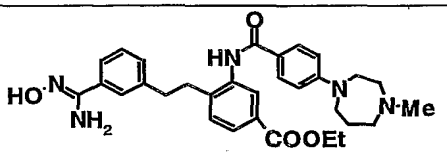
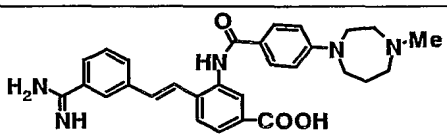
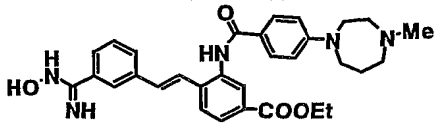
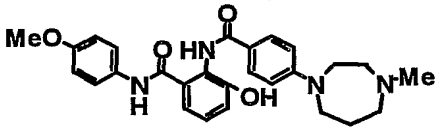
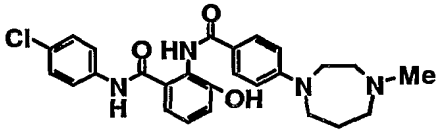
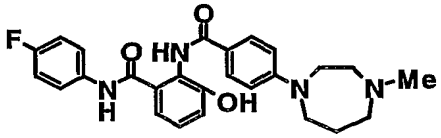
6	 HCl	NMR(DMSO-d_6)： δ：1.32(3H, t, J=7.0Hz), 2.78(3H, s), 4.31(2H, q, J=7.0Hz), 6.86(2H, d, J=8.8Hz), 7.40-7.46(3H, m), 7.53(1H, dt, J=1.9Hz, 7.1Hz), 7.62(1H, s), 7.76(1H, dd, J=1.9Hz, 7.1Hz), 7.90(1H, d, J=1.4Hz), 7.96(2H, d, J=8.8Hz) FAB-MS(m/z)：544 $(M+H)^+$
7	 HCl	NMR(DMSO-d_6)： δ：2.79(3H, d, J = 4.8 Hz), 6.87(2H, d, J = 8.8 Hz), 7.43(1H, d, J = 16.0 Hz), 7.53(1H, d, J = 16.0 Hz), 7.60 - 7.64(1H, m), 7.73(1H, d, J = 8.0 Hz), 7.83(1H, dd, J = 1.6 Hz , 8.4 Hz), 7.89(1H, d, J = 7.6 Hz), FAB-MS(m/z)：498 $(M+H)^+$
8	 HCl	NMR(DMSO-d_6)： δ：1.33(3H, t, J = 7.2 Hz), 2.80(3H, d, J = 4.8 Hz), 4.34(2H, q, J = 7.2 Hz), 6.88(2H, d, J = 9.2 Hz), 7.42 - 7.51(2H, m), 7.58 - 7.65(2H, m), 7.84 - 7.87(2H, m), 7.90(1H, s), 7.96 - 8.01(4H, m) FAB-MS(m/z)：542 $(M+H)^+$
9	 HCl	NMR(DMSO-d_6)： δ：2.10 - 2.41(2H, m), 2.78(3H, s), 3.02 - 3.22(2H, m), 3.35 - 3.57(4H, m), 3.67 - 3.81(4H, m), 3.87 - 3.99(1H, m), 6.80 - 6.95(4H, m), 7.11(1H, d, J = 7.3 Hz), 7.17 - 7.28(2H, m), 7.57(2H, d, J = 8.8 Hz), 7.85 (2H, d, J = 8.8 Hz), 10.02(1H, s), 10.19(1H, s), 10.41(1H, s), 10.64(1H, brs) FAB-MS(m/z)：475 $(M+H)^+$
10	 HCl	NMR(DMSO-d_6)： δ： 2.78(3H, s), 6.84(2H, d, J = 9.3 Hz), 7.10 - 7.13(1H, m), 7.15 - 7.18(1H, m), 7.22 - 7.26(1H, m), 7.36(2H, d, J = 8.8 Hz), 7.71 (2H, d, J = 8.7 Hz), 7.85 (2H, d, J = 8.8 Hz) FAB-MS(m/z)：479 $(M+H)^+$
11	 HCl	NMR(DMSO-d_6)： δ：2.10 - 2.22(1H, m), 2.28 - 2.41(1H, m), 2.77(3H, d, J = 4.9 Hz), 3.02 - 3.21(2H, m), 3.38 - 3.57(4H, m), 3.75(1H, dd, J = 9.7 Hz, 16.1 Hz), 3.93(1H, dd, J = 2.9 Hz, 16.6 Hz), 6.85(2H, d, J = 8.8 Hz), 7.09 - 7.27(5H, m), 7.69(2H, dd, J = 5.1 Hz, 9.1 Hz), 7.85 (2H, d, J = 8.8 Hz), 9.75 - 10.10(1H, br), 10.14(1H, s), 10.36(1H, s), 10.86(1H, brs) FAB-MS(m/z)：463 $(M+H)^+$

表３（続き）

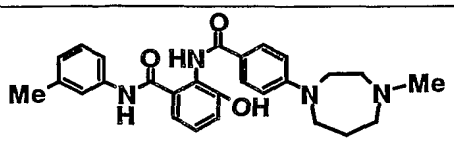
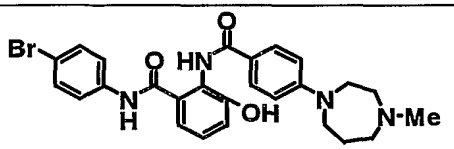
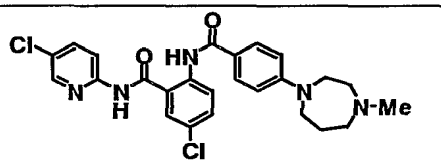
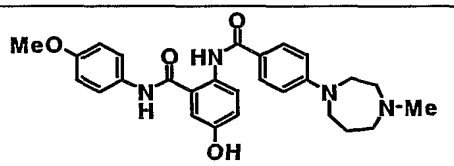
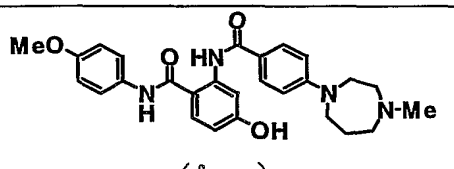
12	 HCl	NMR(DMSO-d_6)： δ：2.11 - 2.40(2H, m), 2.27(3H, s), 2.78(3H, s), 3.01 - 3.22(2H, m), 3.38 - 3.55(4H, m), 3.73(1H, dd, J = 9.7 Hz, 16.1 Hz), 3.93(1H, d, J = 15.1 Hz), 6.83 - 6.91(3H, m), 7.11(1H, dd, J = 1.4 Hz, 8.3 Hz), 7.15 - 7.20(2H, m), 7.24 (1H, t, J = 7.8 Hz), 7.44(1H, d, J = 8.3 Hz), 7.49(1H, s), 7.86(2H, d, J = 8.8 Hz), 9.96(1H, s), 10.14(1H, s), 10.17(1H, s), 10.54(1H, brs) FAB-MS(m/z)：459$(M+H)^+$
13	 HCl	NMR(DMSO-d_6)： δ：2.79(3H, d, J = 2.4 Hz), 6.84(2H, d, J = 9.3 Hz), 7.11(1H, dd, J = 1.3 Hz, 8.1 Hz), 7.16(1H, d. J = 6.8 Hz), 7.24 (1H, t, J = 7.8 Hz), 7.48(2H, d, J = 8.8 Hz), 7.65(2H, d, J = 8.8 Hz), 7.84(2H, d, J = 8.8 Hz), 9.95(1H, s), 9.97(1H, s), 10.39(1H, s), 10.48 - 10.65(1H, br) FAB-MS(m/z)：523$(M+H)^+$
14	 HCl	NMR(DMSO-d_6)： δ：2.12 - 2.20(1H, m), 2.32 - 2.43(1H, m), 2.78(3H, d, J = 4.8 Hz), 3.05 - 3.20(2H, m), 3.39 - 3.56(4H, m), 3.73 - 3.82(1H, m), 3.91 - 3.97(1H, m), 6.90(2H, d, J = 8.7 Hz), 7.65(1H, dd, J = 2.4 Hz , 8.8 Hz), 7.79(2H, d, J = 8.8 Hz), 7.99 - 8.02(2H, m), 8.11 (1H, d, J = 8.8 Hz), 8.43(1H, d, J = 8.8 Hz), 8.48(1H, d, J = 2.5 Hz), 10.94(1H, br s), 11.23(1H, s), 11.29(1H, s) FAB-MS(m/z)：498$(M)^+$
15	 (free)	NMR(DMSO-d_6)： δ：2.25(3H, s), 3.75(3H, s), 6.79(2H, d, J = 8.8 Hz), 6.91 - 7.01(3H, m), 7.24(1H, d, J = 2.5 Hz), 7.61(2H, d. J = 8.8 Hz), 7.69 (2H, d, J = 8.8 Hz), 8.28(1H, d, J = 8.8 Hz), FAB-MS(m/z)：475$(M+H)^+$
16	 (free)	NMR(DMSO-d_6)： δ：2.25 (3H, s), 3.76 (3H, s), 6.55 (1H, dd, J = 8.8, 2.4 Hz), 6.82 (2H, d, J = 9.3 Hz), 6.95 (2H, d, J = 8.8 Hz), 7.57 (2H, d, J = 8.8 Hz), 7.74 (2H, d, J = 9.3Hz), 7.84 (1H, d, J = 8.8 Hz), 8.27 (1H, d, J = 2.4 Hz), FAB-MS(m/z)：475 $(M+H)^+$

表３（続き）

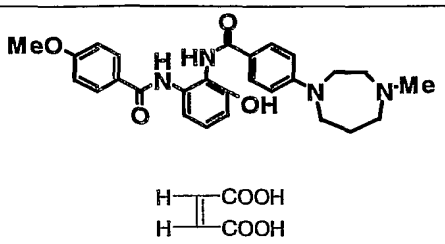
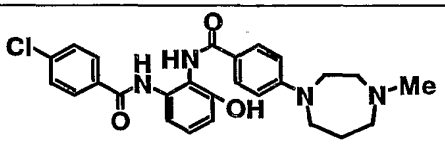
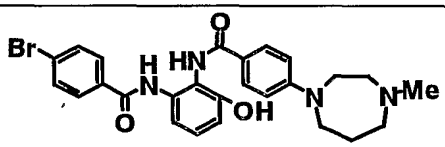
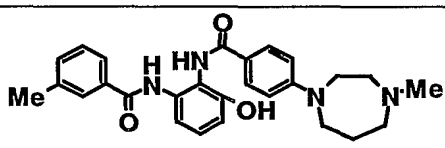
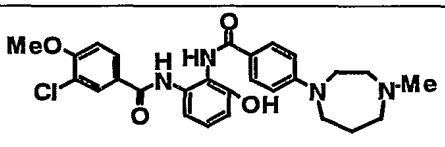
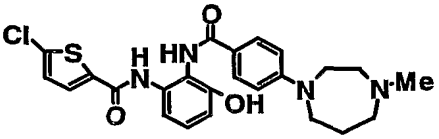
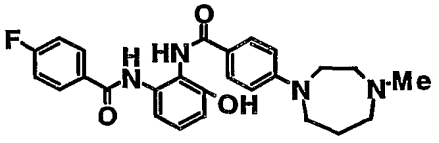
17		NMR(DMSO-d_6)： δ：2.11 - 2.20(2H, m), 2.83(3H, s), 3.20 - 3.45(4H, m), 3.52(2H, t, J = 6.0 Hz), 3.72 - 3.88(5H, m), 6.03(2H, s), 6.80(1H, d, J = 8.0 Hz), 6.85(2H, d, J = 8.8 Hz), 7.04(2H, d, J = 8.8 Hz), 7.14(1H, t, J = 8.0 Hz), 7.24(1H, d, J = 8.0 Hz), 7.85(2H, d, J = 8.8 Hz), 7.91(2H, d, J = 8.8 Hz), 9.47(1H, s), 9.67(1H, s), 9.77(1H, s) FAB-MS(m/z)：475 $(M+H)^+$
18	 HCl	NMR(DMSO-d_6)： δ：2.79(3H, s), 6.82 - 6.86(3H, m), 7.13 - 7.17(1H, m), 7.22(1H, d, J = 8.3 Hz), 7.58(2H, d, J = 8.3 Hz), 7.89 - 7.93(4H, m), FAB-MS(m/z)：479 $(M+H)^+$
19	 HCl	NMR(DMSO-d_6)： δ：2.79(3H, s), 6.82 - 6.86(3H, m), 7.13 - 7.17(1H, m), 7.22(1H, d, J = 7.8 Hz), 7.72(2H, d, J = 8.3 Hz), 7.83(2H, d, J = 8.3 Hz), 7.92(2H, d, J = 8.8 Hz) FAB-MS(m/z)：523 , 525 $(M+H)^+$
20	 HCl	NMR(DMSO-d_6)： δ：2.79(3H, s), 6.82(1H, d, J = 8.3 Hz), 6.86(2H, d, J = 8.8 Hz), 7.13 - 7.17(1H, m), 7.27(1H, d, J = 8.4 Hz), 7.36 - 7.79(2H, m), 7.64 - 7.68(2H, m), 7.95(2H, d, J = 8.3 Hz), 9.56(1H, s) FAB-MS(m/z)：459 $(M+H)^+$
21	 HCl	NMR(DMSO-d_6)： δ：2.69(3H, s), 3.92(3H, s), 6.81 - 6.84(3H, m), 7.14(1H, dd, J = 7.8, 8.3Hz), 7.22(1H, d, J = 7.8Hz), 7.27(1H, d, J = 8.8Hz), 7.88(1H, dd, J = 2.0, 8.3Hz), 7.93(2H, d, J = 8.8)), 7.95(1H, d, J = 2.0Hz) FAB-MS m/z：509 (M^+)
22	 HCl	NMR(DMSO-d_6)： δ：2.80(3H, d, J =3.9 Hz), 6.79 - 6.88(3H, m), 7.10 - 7.18(2H, m), 7.24(1H, d, J = 3.9Hz), 7.72(1H, d, J = 3.9Hz), 7.95(2H, d, J = 8.8Hz), FAB-MS m/z：485 (M^+)
23	 HCl	NMR(DMSO-d_6)： δ：2.78(3H, s), 6.82 - 6.85(3H, m), 7.13 - 7.17(1H, m), 7.22(1H, d, J = 7.8 Hz), 7.32 - 7.37(2H, m), 7.93(2H, d, J = 8.8 Hz), 7.95 - 7.99(2H, m) FAB-MS(m/z)：463(M+H)$^+$

表３（続き）

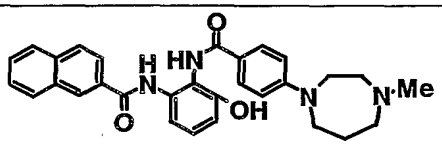
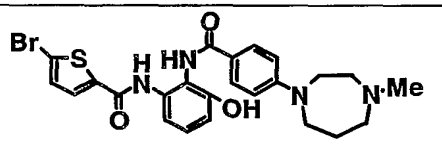
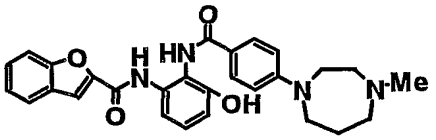
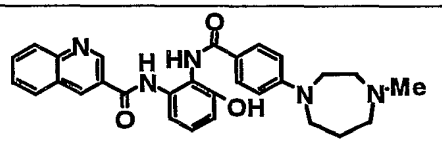
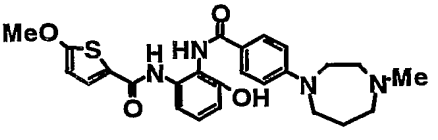
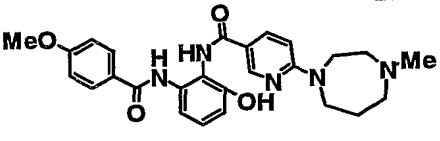
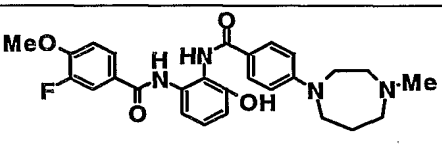
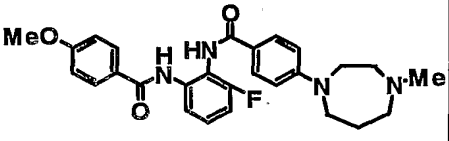
24	 HCl	NMR(DMSO-d_6)： δ：2.76(3H, s), 6.83 - 6.87(3H, m), 7.16 - 7.20(1H, m), 7.31(1H, d, J = 8.3 Hz), 7.59 - 7.66(2H, m), 7.94 - 8.04(6H, m), 8.50(1H, s), FAB-MS(m/z)：495$(M+H)^+$
25	 HCl	NMR(DMSO-d_6)： δ：2.80(3H, d, J =4.3 Hz), 6.81 - 6.86(3H, m), 7.11 - 7.17(2H, m), 7.33(1H, d, J = 3.9Hz), 7.66(1H, d, J = 4.4Hz), 7.94(2H, d, J = 8.8Hz) FAB-MS (m/z)：529, 531 $(M+H)^+$
26	 HCl	NMR(DMSO-d_6)： δ：2.75(3H, s), 6.84 - 6.88(3H, m), 7.15 - 7.19(1H, m), 7.33 - 7.37(2H, m), 7.47 - 7.51(1H, m), 7.57(1H, d, J = 8.3 Hz), 7.67(1H, s), 7.80(1H, d, J = 7.8 Hz), 8.00(2H, d, J = 8.3 Hz) FAB-MS(m/z)：485$(M+H)^+$
27	 HCl	NMR(DMSO-d_6)： δ：2.75(3H, d, J = 4.9 Hz), 6.83(2H, d, J = 9.3 Hz), 6.88(1H, d, J = 7.8Hz), 7.17 - 7.21(1H, m), 7.29(1H, d, J = 7.8 Hz), 7.79 - 7.82(1H, m), 7.98 - 8.01(3H, m), 8.17 - 8.20(2H, m), 9.16(1H, s), 9.44(1H, d, J = 1.9 Hz) FAB-MS (m/z)：496 $(M+H)^+$
28	 HCl	NMR(DMSO-d_6)： δ：2.80(3H, d, J = 2.4 Hz), 6.40(1H, d, J = 3.9 Hz), 6.80(1H, dd, J = 1.5Hz, 7.8Hz), 6.86(2H, d, J = 8.8 Hz), 7.10 - 7.18(2H, m), 7.53(1H, d, J = 3.9 Hz), 7.94(2H, d, J = 8.8Hz) FAB-MS (m/z)：481 $(M+H)^+$
29	 HCl	NMR(DMSO-d_6)： δ：2.79(3H, d, J = 5.9 Hz), 3.81(3H, s), 6.80(1H, d, J = 8.3 Hz), 6.85(1H, d, J = 8.8 Hz), 7.03(2H, d, J = 8.8 Hz), 7.12 - 7.17(1H, m), 7.24- 7.27(1H, m), 7.86(2H, d, J = 8.8 Hz), 8.18(1H, d, J = 8.7 Hz), 8.79(1H, s) FAB-MS(m/z)：476 $(M+H)^+$
30	 HCl	NMR(DMSO-d_6)： δ：2.79(3H, s), 6.82 - 6.86(3H, m), 7.12 - 7.16(1H, m), 7.22(1H, d, J = 7.8 Hz), 7.27 - 7.31(1H, m), 7.72 - 7.77(2H, m), 7.94(2H, d, J = 8.3 Hz), FAB-MS(m/z)：493$(M+H)^+$
31	 HCl	NMR(DMSO-d_6)： δ：2.79(3H, d, J = 5.9 Hz), 3.05 - 3.21(2H, m), 3.82(3H, s), 6.85(2H, d, J = 9.3 Hz), 7.03(2H, d, J = 8.8 Hz), 7.13 - 7.18(1H, m), 7.31 - 7.37(1H, m), 7.55 - 7.59(1H, m), 7.89(2H, d, J = 8.8 Hz), 7.94(2H, d, J = 8.7 Hz) FAB-MS(m/z)：477$(M+H)^+$

表３（続き）

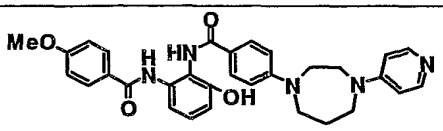
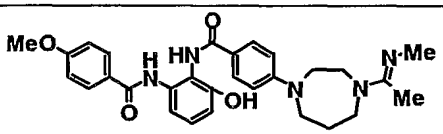
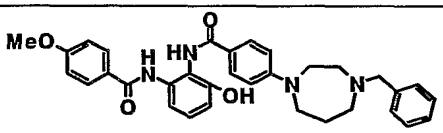
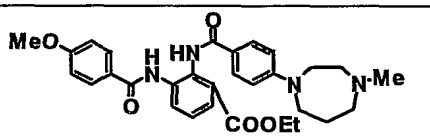
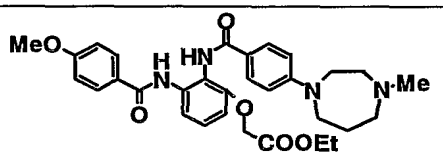
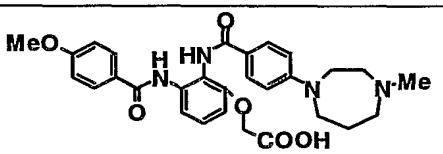
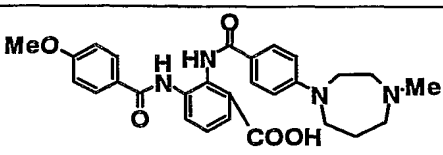
32	 HCl	NMR(DMSO-d_6): δ:1.82 - 2.01(2H, m), 3.46 - 3.89(11H, m), 6.80(1H, d, J = 7.8 Hz), 6.86(2H, d, J = 8.8 Hz), 6.97 - 7.21(5H, m), 7.25(1H, d, J = 8.3 Hz), 7.78 - 7.94(4H, m), 8.18(2H, s), 9.51(1H, s), 9.66(1H, brs), 9.82(1H, s), 13.46(1H, brs), FAB-MS(m/z): 538$(M+H)^+$
33	 HCl	NMR(DMSO-d_6): δ:2.24(1.5H, s), 2.26(1.5H, s), 2.84 - 2.95(3H, m), 6.81(1H, d, J = 7.8 Hz), 6.84 - 6.93(2H, m), 7.04(2H, d, J = 8.8 Hz), 7.14(1H, t, J = 8.3 Hz), 7.24(1H, d, J = 8.3 Hz), 7.87(2H, d, J = 8.8 Hz), 7.91(2H, d, J = 8.9 Hz) FAB-MS(m/z): 516$(M+H)^+$
34	 HCl	NMR(DMSO-d_6): δ:6.80 (1H, dd, J = 0.9 Hz, 8.3 Hz), 6.85(2H, d, J = 8.7 Hz), 7.03(2H, d, J = 8.7 Hz), 7.14(1H, t, J = 8.3 Hz), 7.24(1H, d, J = 7.8 Hz), 7.43 - 7.51(3H, m), 7.54 - 7.61(2H, m), 7.86(2H, d, J = 8.7 Hz), 7.91(2H, d, J = 8.7 Hz) FAB-MS(m/z): 551$(M+H)^+$
35	 HCl	NMR(DMSO-d_6): δ: 1.14(3H, t, J = 6.8 Hz), 2.80(3H, d, J = 4.4 Hz), 3.83(3H, s), 4.16(2H, q, J = 7.2 Hz), 6.86(2H, d, J = 8.8 Hz), 7.06(2H, d, J = 8.8 Hz), 7.39 - 7.43(1H, m), 7.68(1H, dd, J = 1.5 Hz , 7.8 Hz), 7.86 - 7.88(3H, m), 7.94(2H, d, J = 8.7 Hz) FAB-MS(m/z): 531$(M+H)^+$
36	 HCl	NMR(DMSO-d_6): δ: 1.21(3H, t, J =7.3 Hz), 2.78(3H, d, J = 4.9 Hz), 4.17(2H, q, J = 7.3 Hz), 4.83(2H, s), 6.86(2H, d, J = 9.3 Hz), 6.92(1H, d, J = 7.3 Hz), 7.04(2H, d, J = 8.8 Hz), 7.25 - 7.29(1H, m), 7.49(1H, d, J = 7.8 Hz), 7.86(2H, d, J = 8.8 Hz), 7.93(2H, d, J = 8.8 Hz) FAB-MS(m/z): 561$(M+H)^+$
37	 HCl	NMR(DMSO-d_6): δ: 2.78(3H, s), 4.75(2H, s), 6.86(2H, d, J = 9.3 Hz), 6.94(1H, d, J = 7.3 Hz), 7.04(2H, d, J = 8.8 Hz), 7.25 - 7.30(1H, m), 7.50(1H, d, J = 7.9 Hz), 7.85(2H, d, J = 8.8 Hz), 7.95(2H, d, J = 8.8 Hz) FAB-MS(m/z): 533$(M+H)^+$
38	 HCl	NMR(DMSO-d_6): δ: 2.77(3H, d, J = 4.4 Hz), 6.87(2H, d, J = 8.7 Hz), 7.05(2H, d, J = 8.8 Hz), 7.38 - 7.42(1H, m), 7.75(1H, d, J = 7.3 Hz), 7.88 - 7.94(5H, m) FAB-MS(m/z): 503$(M+H)^+$

表３（続き）

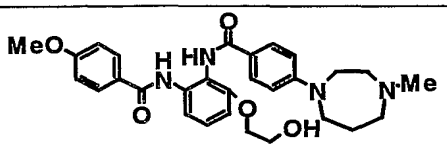
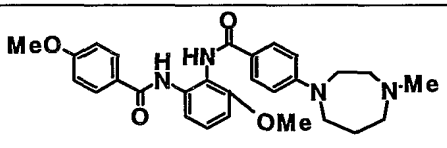
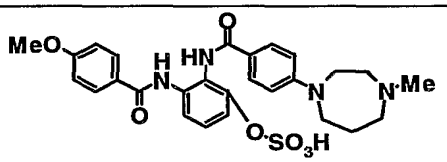
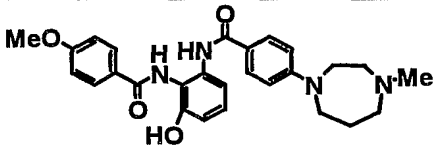
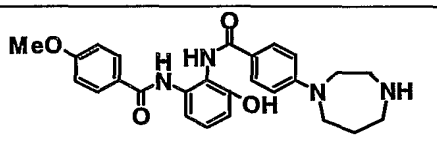
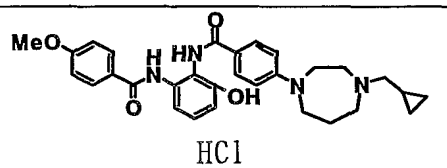
39	 HCl	NMR(DMSO-d_6)： δ：2.12 - 2.22(1H, m), 2.26 - 2.39(1H, m), 2.79(3H, d, J = 3.9 Hz), 3.05 - 3.21(2H, m), 3.39 - 3.55(4H, m), 3.66 - 3.79(3H, m), 3.81(3H, s), 3.90 - 3.97(1H, m), 4.11(2H, t, J = 4.9 Hz), 4.86(1H, br s), 6.86(2H, d, J = 8.8 Hz), 6.97(1H, d, J = 7.4 Hz), 7.04(2H, d, J = 8.8 Hz), 7.25 - 7.29(1H, m), 7.42(1H, d, J = 8.3 Hz), 7.86(2H, d, J = 8.7 Hz), 7.92(2H, d, J = 8.8 Hz), 9.55(1H, s), 9.89(1H, s), 10.67(1H, br s) FAB-MS(m/z)：519$(M+H)^+$
40	 HCl	NMR(DMSO-d_6)： δ：2.79(3H, d, J = 4.9 Hz), 6.85(2H, d, J = 8.8 Hz), 6.95(1H, d, J = 8.3 Hz), 7.02(2H, d, J = 8.7 Hz), 7.29(1H, t, J = 8.3 Hz), 7.42(1H, d, J = 8.3 Hz), 7.84(2H, d, J = 8.8 Hz), 7.92(2H, d, J = 8.8 Hz) FAB-MS(m/z)：489 $(M+H)^+$
41	 (free)	NMR(DMSO-d_6)： δ：2.08 - 2.23(2H, m), 2.84(3H, s), 3.10 - 4.05(11H, m), 6.93(2H, d, J = 9.3 Hz), 6.95(1H, d, 8.3 Hz), 7.01-7.08(3H, m), 7.28(1H, t, J = 8.3 Hz), 7.7(1H, dd, J = 1.4 Hz, 8.3 Hz), 7.83(2H, d, J = 8.8 Hz), 7.92(2H, d, J = 9.2Hz), 9.4(1H, brs), 9.91(1H, s), 10.37(1H, s) FAB-MS(m/z)：553 $(M-H)^+$
42	 HCl	NMR(DMSO-d_6)： δ：2.79(3H, d = 4.9 Hz), 6.78(1H, d, J = 7.8 Hz), 6.82(2H, d, J = 8.8 Hz), 7.06(2H, d, J = 8.8 Hz), 7.13(1H, t, J = 7.8 Hz), 7.30(1H, d, J = 7.8 Hz), 7.75(2H, d, J = 8.8 Hz), 8.01(2H, d, J = 8.8 Hz), FAB-MS(m/z)：475$(M+H)^+$
43	 HCl	NMR(DMSO-d_6)： δ：6.81(1H, dd, J = 1.5, 8.3 Hz), 6.86(2H, d, J = 8.8 Hz), 7.03(2H, d, J = 8.7 Hz), 7.13(1H, t, J = 8.3 Hz), 7.25(1H, d, J = 8.3 Hz), 7.87(2H, d, J = 8.8 Hz), 7.93(2H, d, J = 8.8 Hz), FAB-MS(m/z)：461$(M+H)^+$
44	 HCl	NMR(DMSO-d_6)： δ：0.35 - 0.43(2H, m), 0.61 - 0.67(2H, m), 1.08 - 1.15(1H, m)6.81(1H, dd, J = 1.0 Hz , 8.8 Hz), 6.86(2H, d, J = 8.8 Hz), 7.03(2H, d, J = 8.3 Hz), 7.11 - 7.16(1H, m), 7.24(1H, dd, J = 1.0 Hz , 7.9 Hz), 7.87(2H, d, J = 8.8 Hz), 7.93(2H, d, J = 8.8 Hz), FAB-MS(m/z)：515$(M+H)^+$

表３（続き）

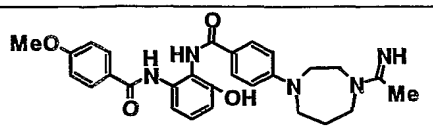
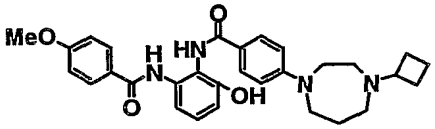
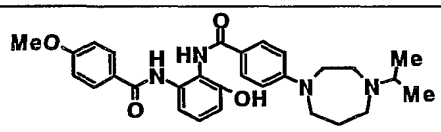
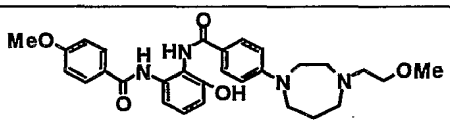
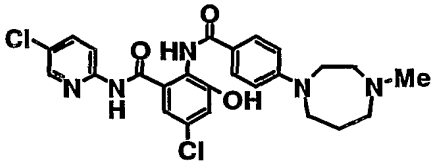
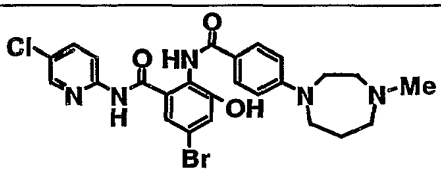
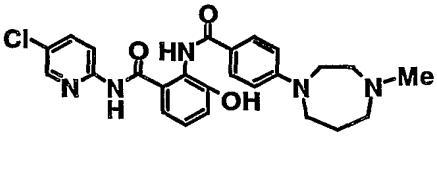
45	 HCl	NMR(DMSO-d_6)： δ:6.81(1H, d, J = 8.3 Hz), 6.84 - 6.93(2H, m), 7.03(2H, d, J = 9.3 Hz), 7.13(1H, t, J = 8.3 Hz), 7.25(1H, d, J = 8.3 Hz), 7.88(2H, d, J = 8.2 Hz), 7.92(2H, d, J = 8.3 Hz) FAB-MS(m/z)：502$(M+H)^+$
46	 HCl	NMR(DMSO-d_6)： δ：6.80 - 6.86(3H, m), 7.03(2H, d, J = 8.8 Hz), 7.11 - 7.16(1H, m), 7.24(1H, dd, J = 1.0 Hz , 7.8 Hz), 7.87(2H, d, J = 8.8 Hz), 7.93(2H, d, J = 8.8 Hz) FAB-MS(m/z)：515$(M+H)^+$
47	 HCl	NMR(DMSO-d_6)： δ:1.21 - 1.28(6H, m), 6.80(1H, d, J = 7.9 Hz), 6.85(2H, d, J = 8.8 Hz), 7.03(2H, d, J = 8.8 Hz), 7.14(1H, t, J = 7.9 Hz), 7.24(1H, d, J = 7.8 Hz), 7.86(2H, d, J = 8.3 Hz), 7.92(2H, d, J = 8.8 Hz) FAB-MS(m/z)：503$(M+H)^+$
48	 HCl	NMR(DMSO-d_6)： δ:6.73 - 6.88(3H, m), 7.03(2H, d, J = 8.8 Hz), 7.14(1H, t, J = 8.3 Hz), 7.24(1H, dd, J = 1.4 Hz, 8.3 Hz), 7.87(2H, d, J = 8.8 Hz), 7.93(2H, d, J = 8.8 Hz), FAB-MS(m/z)：519$(M+H)^+$
49	 HCl	NMR(DMSO-d_6)： δ:2.10 - 2.21(1H, m), 2.23 - 2.37(1H, m), 2.79(3H, d, J = 4.9 Hz), 3.02 - 3.21(2H, m), 3.37 - 3.56(4H, m), 3.66 - 3.95(2H, m), 6.81(2H, d, J = 8.8 Hz), 7.15(2H, s), 7.82(2H, d, J = 8.8 Hz), 7.89(1H, dd, J = 2.5, 8.8 Hz), 8.08(1H, d, J = 8.8 Hz), 8.36(1H, d, J = 2.4 Hz), 9.51(1H, s), 10.33 - 10.63(2H, br), 10.68(1H, s) FAB-MS(m/z)：514$(M+H)^+$
50	 HCl	NMR(DMSO-d_6)： δ:2.10 - 2.33(2H, m), 2.79(3H, s), 3.01 - 3.22(2H, m), 3.35 - 3.51(4H, m), 3.65 - 3.79(1H, m), 3.85 - 3.98(1H, m), 6.81(2H, d, J = 8.8 Hz), 7.27(2H, s), 7.82(2H, d, J = 9.3 Hz), 7.89(1H, dd, J = 2.5, 8.8 Hz), 8.08(1H, d, J = 9.2 Hz), 8.36(1H, d, J = 2.9 Hz), 9.50(1H, s), 10.37(1H, brs), 10.44(1H, s), 10.69(1H, s) FAB-MS(m/z)：558, 560$(M+H)^+$
51	 HCl	NMR(DMSO-d_6)： δ：2.22(2H, brs), 2.74(3H, s), 3.00 - 3.60(6H, m), 3.81(2H, brs), 6.82(2H, d, J = 9.3 Hz), 7.10 - 7.25(3H, m), 7.83(2H, d, J = 8.8 Hz), 7.90(1H, dd, J = 2.8 Hz, 9.1 Hz), 8.13(1H, d, J = 8.7 Hz), 8.35(1H, d, J = 2.5 Hz), 9.71(1H, s), 9.95(1H, s), 10.58(1H, s), 10.62 - 10.88(1H, br) FAB-MS(m/z)：480$(M+H)^+$

表３（続き）

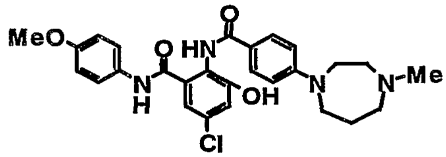
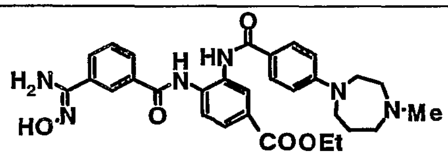
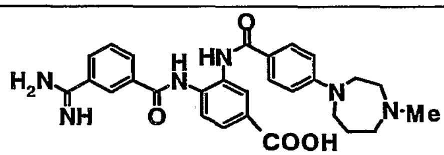
52	 HCl	NMR(DMSO-d_6): δ:2.10 - 2.34(2H, m), 2.81(3H, s), 3.01 - 3.25(2H, m), 3.35 - 3.60(4H, m), 3.62 - 3.79(4H, m), 3.82 - 4.00(1H, m), 6.84(2H, d, J = 9.3 Hz), 6.88(2H, d, J = 8.8 Hz), 7.12(1H, d, J = 2.5 Hz), 7.18(1H, d, J = 2.4 Hz), 7.54(2H, d, J = 9.3 Hz), 7.84(2H, d, J = 8.8 Hz), 9.86(1H, brs), 9.96(1H, s), 10.16(1H, s), 10.43(1H, s) FAB-MS(m/z): 509(M+H)$^+$
53	 HCl	NMR(DMSO-d_6): δ: 1.35(3H, t, J = 7.3 Hz), 2.79(3H, d, J = 4.9 Hz), 4.35(2H, q, J = 7.3 Hz), 6.85(2H, d, J = 9.3 Hz), 7.68 - 7.74(1H, m), 7.82 - 7.88(2H, m), 7.92 - 7.98(3H, m), 8.19 - 8.24(1H, m), 8.27(1H, s), 8.38 (1H, s) FAB-MS(m/z): 559 (M+H)$^+$
54	 HCl	NMR(DMSO-d_6): δ: 2.79(3H, d, J = 4.9 Hz), 6.85(2H, d, J = 9.3 Hz), 7.76 - 7.84(3H, m), 7.98(2H, d, J = 8.8 Hz), 8.03(1H, d, J = 7.8 Hz), 8.25(1H, s), 8.31(1H, d, J = 7.8 Hz), 8.53(1H, s), FAB-MS(m/z): 515 (M+H)$^+$

表４

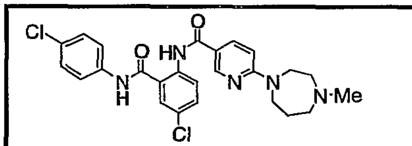
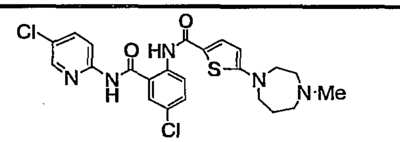
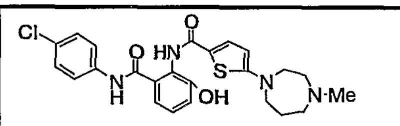
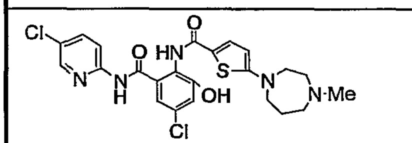
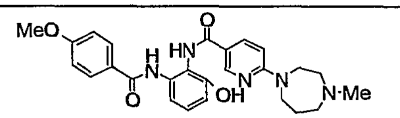
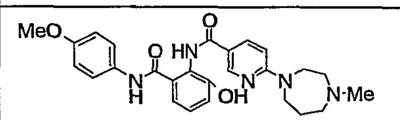
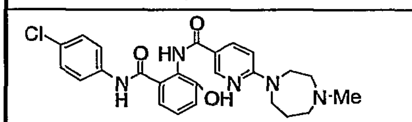
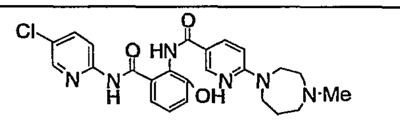
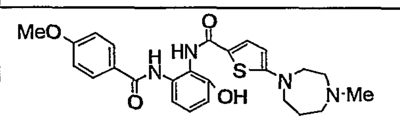
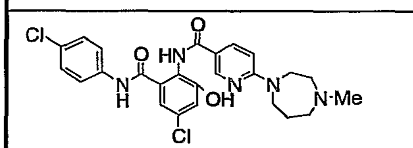
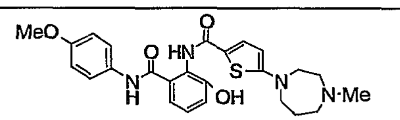
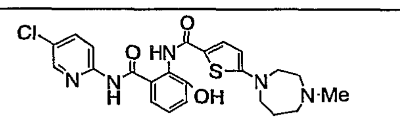
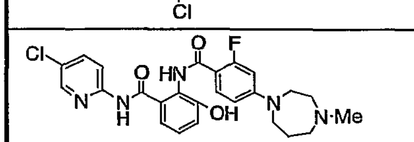
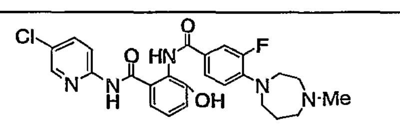
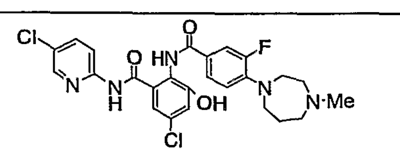
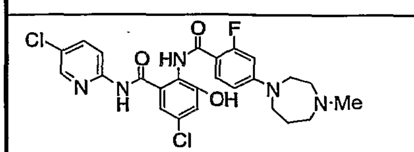
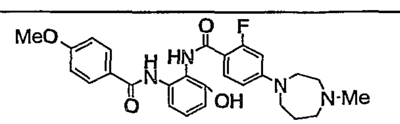
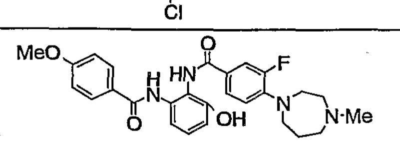
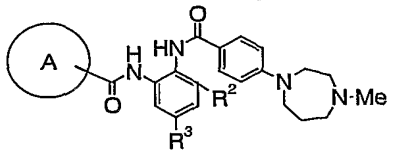
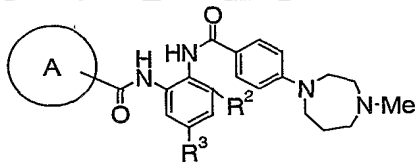
		
		
		
		
		
		

表 5



No.	A	R^2	R^3	No.	A	R^2	R^3
1		OH	Cl	32		OH	Cl
2		OH	H	33		H	Cl
3		H	Cl	34		OH	Br
4		OH	Br	35		H	Br
5		H	Br	36		OH	Cl
6		OH	F	37		H	Cl
7		H	F	38		OH	Br
8		OH	Cl	39		H	Br
9		OH	H	40		OH	Cl
10		H	Cl	41		H	Cl
11		OH	Br	42		OH	Br
12		H	Br	43		H	Br
13		OH	F	44		OH	Cl
14		H	F	45		H	Cl
15		OH	Cl	46		OH	Br
16		H	Cl	47		H	Br
17		OH	Br	48		OH	H
18		H	Br	49		OH	Cl
19		OH	Cl	50		H	Cl
20		H	Cl	51		OH	Br
21		OH	Br	52		H	Br
22		H	Br	53		OH	H
23		OH	H	54		OH	Cl
24		OH	Cl	55		H	Cl
25		H	Cl	56		OH	Br
26		OH	Br	57		H	Br
27		OH	H	58		OH	H
28		OH	Cl	59		OH	Cl
29		OH	H	60		OH	H
30		H	Cl	61		H	Cl
31		OH	Br	62		OH	Br

表５（続き）



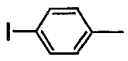
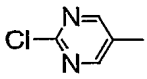
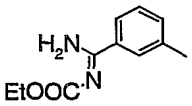
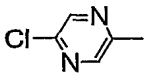
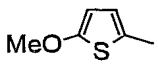
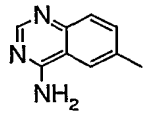
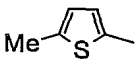
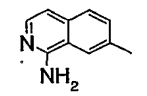
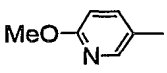
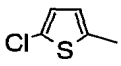
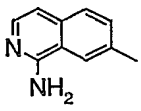
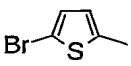
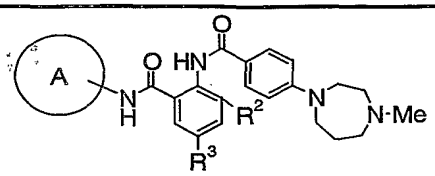
No.	A	R^2	R^3	No.	A	R^2	R^3
63		OH	Cl	92		OH	Cl
64		OH	H	93		OH	H
65		H	Cl	94		H	Cl
66		OH	Br	95		OH	Br
67		H	Br	96		H	Br
68		OH	Cl	97		OH	Cl
69		OH	H	98		OH	H
70		H	Cl	99		H	Cl
71		OH	Br	100		OH	Br
72		H	Br	101		H	Br
73		OH	Cl	102		OH	Cl
74		OH	H	103		OH	H
75		H	Cl	104		H	Cl
76		OH	Br	105		OH	Br
77		H	Br	106		H	Br
78		OH	Cl	107		OH	Cl
79		H	Cl	108		OH	H
80		OH	Br	109		H	Cl
81		H	Br	110		OH	Br
82		OH	Cl	111		H	Br
83		OH	H	112		OH	Cl
84		H	Cl	113		H	Cl
85		OH	Br	114		OH	Br
86		H	Br	115		H	Br
87		OH	Cl	116		OH	Cl
88		OH	H	117		H	Cl
89		H	Cl	118		OH	Br
90		OH	Br	119		H	Br
91		H	Br	120		OH	F

表５（続き）

No.	A	R^2	R^3	No.	A	R^2	R^3
121		OH	Cl	151		H	Cl
122		OH	H	152		OH	Br
123		H	Cl	153		H	Br
124		OH	Br	154		OH	F
125		H	Br	155		OH	Cl
126		OH	F	156		H	Cl
127		H	F	157		OH	Br
128		OH	Cl	158		H	Br
129		OH	H	159		OH	Cl
130		H	Cl	160		H	Cl
131		OH	Br	161		OH	Br
132		H	Br	162		H	Br
133		OH	Cl	163		H	Br
134		H	Cl	164		OH	F
135		OH	Br	165		OH	Cl
136		H	Br	166		H	Cl
137		OH	Cl	167		OH	Br
138		H	Cl	168		H	Br
139		OH	Br	169		OH	H
140		H	Br	170		OH	Cl
141		OH	H	171		H	Cl
142		OH	Cl	172		OH	Br
143		H	Cl	173		H	Br
144		OH	Br	174		OH	H
145		H	Br	175		OH	F
146		OH	H	176		OH	Cl
147		OH	Cl	177		H	Cl
148		OH	H	178		OH	Br
149		OH	Br	179		H	Br
150		H	Cl	180		OH	H

表５（続き）



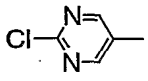
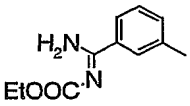
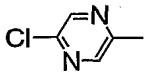
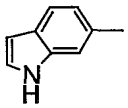
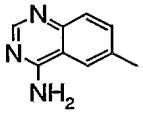
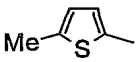
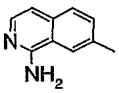
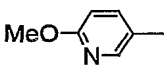
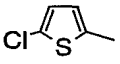
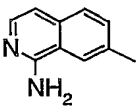
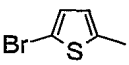
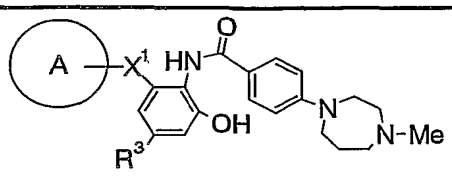
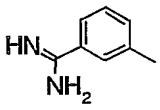
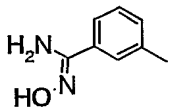
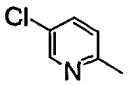
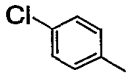
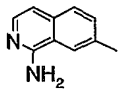
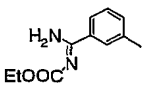
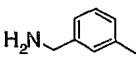
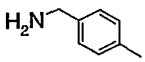
No.	A	R^2	R^3	No.	A	R^2	R^3
181		OH	Cl	211		OH	Cl
182		OH	H	212		OH	H
183		H	Cl	213		H	Cl
184		OH	Br	214		OH	Br
185		H	Br	215		H	Br
186		OH	Cl	216		OH	Cl
187		OH	H	217		OH	H
188		H	Cl	218		H	Cl
189		OH	Br	219		OH	Br
190		H	Br	220		H	Br
191		OH	Cl	221		OH	Cl
192		OH	H	222		OH	H
193		H	Cl	223		H	Cl
194		OH	Br	224		OH	Br
195		H	Br	225		H	Br
196		OH	Cl	226		OH	Cl
197		OH	H	227		OH	H
198		H	Cl	228		H	Cl
199		OH	Br	229		OH	Br
200		H	Br	230		H	Br
201		OH	Cl	231		OH	Cl
202		OH	H	232		H	Cl
203		H	Cl	233		OH	Br
204		OH	Br	234		H	Br
205		H	Br	235		OH	H
206		OH	Cl	236		OH	Cl
207		OH	H	237		H	Cl
208		H	Cl	238		OH	Br
209		OH	Br	239		H	Br
210		H	Br	240		OH	H

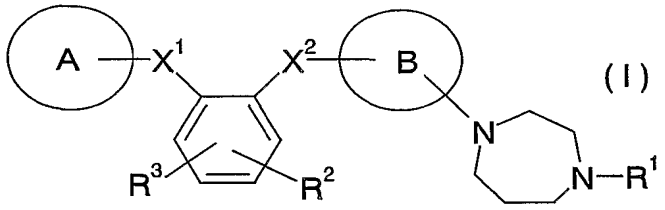
表6



No	A	X^1	R^3	No	A	X^1	R^3
1		$-CH_2-CH_2-$	H	32		$-CH_2-CH_2-$	H
2		$-CH_2-CH_2-$	Cl	33		$-CH_2-CH_2-$	Cl
3		$-NH-CH_2-$	H	34		$-NH-CH_2-$	H
4		$-NH-CH_2-$	Cl	35		$-NH-CH_2-$	Cl
5		$-O-CH_2-$	H	36		$-O-CH_2-$	H
6		$-O-CH_2-$	Cl	37		$-O-CH_2-$	Cl
7		(E) -CH=CH-	H	38		(E) -CH=CH-	H
8		(E) -CH=CH-	Cl	39		(E) -CH=CH-	Cl
9		$-CH_2-CH_2-$	H	40		$-CH_2-CH_2-$	H
10		$-CH_2-CH_2-$	Cl	41		$-CH_2-CH_2-$	Cl
11		$-NH-CH_2-$	H	42		$-NH-CH_2-$	H
12		$-NH-CH_2-$	Cl	43		$-NH-CH_2-$	Cl
13		$-O-CH_2-$	H	44		$-O-CH_2-$	H
14		$-O-CH_2-$	Cl	45		$-O-CH_2-$	Cl
15		(E) -CH=CH-	Cl	46		(E) -CH=CH-	Cl
16		$-CH_2-CH_2-$	H	47		$-CH_2-CH_2-$	H
17		$-CH_2-CH_2-$	Cl	48		$-CH_2-CH_2-$	Cl
18		$-NH-CH_2-$	H	49		$-NH-CH_2-$	H
19		$-NH-CH_2-$	Cl	50		$-NH-CH_2-$	Cl
20		$-O-CH_2-$	H	51		$-O-CH_2-$	H
21		$-O-CH_2-$	Cl	52		$-O-CH_2-$	Cl
22		(E) -CH=CH-	H	53		(E) -CH=CH-	H
23		(E) -CH=CH-	Cl	54		(E) -CH=CH-	Cl
24		$-CH_2-CH_2-$	H	55		$-CH_2-CH_2-$	H
25		$-CH_2-CH_2-$	Cl	56		$-CH_2-CH_2-$	Cl
26		$-NH-CH_2-$	H	57		$-NH-CH_2-$	H
27		$-NH-CH_2-$	Cl	58		$-NH-CH_2-$	Cl
28		$-O-CH_2-$	H	59		$-O-CH_2-$	H
29		$-O-CH_2-$	Cl	60		$-O-CH_2-$	Cl
30		(E) -CH=CH-	H	61		(E) -CH=CH-	H
31		(E) -CH=CH-	Cl	62		(E) -CH=CH-	Cl

請求の範囲

1．下記一般式（Ｉ）で示されるジアゼパン誘導体又はその塩。



（上記式中の記号は、それぞれ以下の意味を有する。

A環、及びB環：同一又は異なって１～３個の置換基をそれぞれ有しても良いアリール、又はヘテロアリール、

X^1：-C(=O)-NR^4-、-NR^4-C(=O)-、-NR^4-CH_2-、-O-CH_2-、-CH_2-CH_2-、又は-CH=CH-、

X^2：-C(=O)-NR^5-、又は-NR^5-C(=O)-、

R^1：水素原子、低級アルキル、-低級アルキレン-O-低級アルキル、C_{3-8}シクロアルキル、アリール、ヘテロアリール、-低級アルキレン-C_{3-8}シクロアルキル、-低級アルキレン-アリール、-低級アルキレン-ヘテロアリール、又は-C(=NR^6)-低級アルキル、

R^2：-OH、-O-低級アルキル、-O-低級アルキレン-OH、-O-SO_2-OH、-O-低級アルキレン-COOH、-O-低級アルキレン-COO-低級アルキル、-COOH、-COO-低級アルキル、又はハロゲン原子、

R^3：水素原子、ハロゲン原子、又は低級アルキル、

R^4、R^5、及びR^6：同一又は異なって水素原子、又は低級アルキル）

2．R^2が-OHである請求の範囲１記載のジアゼパン誘導体又はその塩。

3．A環、及びB環が同一又は異なって１～３個の置換基をそれぞれ有しても良いベンゼン環、ピリジン環、ナフタレン環、チオフェン環、ベンゾフラン環、又はキノリン環である請求の範囲１記載のジアゼパン誘導体又はその塩。

４．１～３個の置換基をそれぞれ有しても良いアリール、又はヘテロアリールの置換基が、置換基を有しても良い低級アルキル、低級アルケニル、低級アルキニル、C_{3-8}シクロアルキル、-O-置換基を有しても良い低級アルキル、ハロゲン原子、-NH_2、-NH-低級アルキル、-N-(低級アルキル)$_2$、-C(=NH)-NH_2、-C(=N-OH)-NH_2、-C(=NH)-NH-OH、-C(=NH)-NH-C(=O)-O-低級アルキル、-COOH、-C(=O)-O-置換基を有しても良い低級アルキル、-C(=O)-O-置換基を有しても良いC_{6-14}アリール、-C(=O)-O-置換基を有しても良いヘテロアリール、-CN、-NO_2、-OH、-O-CO-置換基を有しても良い低級アルキル、-O-CO-NH_2、-O-CO-NH-低級アルキル、-O-CO-N-(低級アルキル)$_2$、-SH、-C(=O)-NH_2、-C(=O)-NH-(低級アルキル)、-C(=O)-N-(低級アルキル)$_2$から選択される置換基である請求の範囲１記載のジアゼパン誘導体又はその塩。

５．３－ヒドロキシ－4'－メトキシ－２－｛［４－（４－メチル－１，４－ジアゼパン－１－イル）ベンゾイル］アミノ｝ベンズアニリド、３－ヒドロキシ－N^1－（４－メトキシベンゾイル）－N^2－［４－（４－メチル－１，４－ジアゼパン－１－イル）ベンゾイル］－１，２－フェニレンジアミン、５－クロロ－*N*－（５－クロロ－２－ピリジル）－３－ヒドロキシ－２－｛［４－（４－メチル－１，４－ジアゼパン－１－イル）ベンゾイル］アミノ｝ベンズアミド、５－クロロ－３－ヒドロキシ－4'－メトキシ－２－｛［４－（４－メチル－１，４－ジアゼパン－１－イル）ベンゾイル］アミノ｝ベンズアニリド、５－ブロモ－*N*－（５－クロロ－２－ピリジル）－３－ヒドロキシ－２－｛［４－（４－メチル－１，４－ジアゼパン－１－イル）ベンゾイル］アミノ｝ベンズアミドから選択される請求の範囲１記載のジアゼパン誘導体又はその塩。

６．請求の範囲１に記載されるジアゼパン誘導体又はその塩を有効成分とする医薬組成物。

７．請求の範囲１に記載されるジアゼパン誘導体又はその塩を有効成分とする活性化血液凝固第Ｘ因子阻害剤。

INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP01/02673

A. CLASSIFICATION OF SUBJECT MATTER
Int.Cl[7] C07D243/08, C07D401/04, C07D401/12, C07D403/12, C07D405/12, C07D409/04, C07D409/12, C07D409/14, C07D471/04 104, A61K7/02, A61K31/551

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
Int.Cl[7] C07D243/08, C07D401/04, C07D401/12, C07D403/12, C07D405/12, C07D409/04, C07D409/12, C07D409/14, C07D471/04 104, A61K7/02, A61K31/551

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
CA(STN),REGISTRY(STN),WPIDS(STN)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO, 99/37643, A (YAMANOUCHI PHARMACEUTICAL CO., LTD.), 29 July, 1999 (29.07.99), the whole document & AU, 9920746, A	1-7

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
24 April, 2001 (24.04.01)	15 May, 2001 (15.05.01)
Name and mailing address of the ISA/ Japanese Patent Office	Authorized officer
Facsimile No.	Telephone No.

国際調査報告

国際出願番号　PCT／JP01／02673

A.　発明の属する分野の分類（国際特許分類（IPC））

Int cl[7] C07D243／08, C07D401／04, C07D401／12, C07D403／12, C07D405／12, C07D409／04, C07D409／12, C07D409／14, C07D471／04 104, A61K7／02, A61K31／551

B.　調査を行った分野

調査を行った最小限資料（国際特許分類（IPC））

Int cl[7] C07D243／08, C07D401／04, C07D401／12, C07D403／12, C07D405／12, C07D409／04, C07D409／12, C07D409／14, C07D471／04 104, A61K7／02, A61K31／551

最小限資料以外の資料で調査を行った分野に含まれるもの

国際調査で使用した電子データベース（データベースの名称、調査に使用した用語）

CA（STN），REGISTRY（STN），WPIDS（STN）

C.　関連すると認められる文献

引用文献のカテゴリー＊	引用文献名　及び一部の箇所が関連するときは、その関連する箇所の表示	関連する請求の範囲の番号
A	WO，99／37643，A（山之内製薬株式会社）29．7月．1999（29．07．99），文献全体　＆　AU，9920746，A	1－7

☐ C欄の続きにも文献が列挙されている。

☐ パテントファミリーに関する別紙を参照。

＊　引用文献のカテゴリー

「A」特に関連のある文献ではなく、一般的技術水準を示すもの

「E」国際出願日前の出願または特許であるが、国際出願日以後に公表されたもの

「L」優先権主張に疑義を提起する文献又は他の文献の発行日若しくは他の特別な理由を確立するために引用する文献（理由を付す）

「O」口頭による開示、使用、展示等に言及する文献

「P」国際出願日前で、かつ優先権の主張の基礎となる出願の日の後に公表された文献

「T」国際出願日又は優先日後に公表された文献であって出願と矛盾するものではなく、発明の原理又は理論の理解のために引用するもの

「X」特に関連のある文献であって、当該文献のみで発明の新規性又は進歩性がないと考えられるもの

「Y」特に関連のある文献であって、当該文献と他の1以上の文献との、当業者にとって自明である組合せによって進歩性がないと考えられるもの

「&」同一パテントファミリー文献

国際調査を完了した日	国際調査報告の発送日
24．04．01	15.05.01

国際調査機関の名称及びあて先	特許庁審査官（権限のある職員）		
日本国特許庁（ISA／JP） 郵便番号100－8915 東京都千代田区霞が関三丁目4番3号	内藤　伸一	4P	8615
	電話番号　03－3581－1101　内線　3492		